ANOXIA

ITS EFFECT ON THE BODY

By

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To my wife and daughter

ALICE *and* WILHELMINA

PREFACE

A number of treatises dealing with the effect of oxygen want on the body have been written. As far as the author is aware, however, no writer has taken up systematically and in any detail the effect of anoxia on all the known physiologic processes of the body. This the writer has tried to do; an attempt has been made to assemble the important facts which are known concerning the effect of oxygen want on the body.

During the last twenty-five years or so, a vast amount of research work has been done in the field of anoxia. When it is realized that diseases of the heart, circulation, the blood, and the lungs may all cause oxygen want, the importance of the subject becomes obvious.

The ever increasing popularity of travel by air and the importance of the airplane in war have made the subject of oxygen want of interest even to the layman. It was not so long ago that virtually the only people subjected to rarefied air were the amateur and professional mountain-climbers and the occasional balloonist. These people represented but a small percentage of the population. All this is now changed; today a great number of individuals are subjected daily to an environment which may produce oxygen want. Physicians, too, are recognizing more and more that anoxemia is a concomitant symptom of many diseases.

It is only when an attempt is made to bring together the known facts concerning a subject that one becomes especially cognizant of the many gaps in the particular field of knowledge to which it belongs. While, as previously mentioned, there has been a tremendous amount of research done in the field of anoxia in the past few years, many problems still remain unsolved. The author hopes that this monograph will stimulate a keen interest in solving some of the fascinating problems in this field and that the solution of them not only will add to the sum total of human knowledge but will be of direct benefit to the science of aviation and, still more important, to the alleviation of suffering caused by disease.

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HISTORICAL

It is not the intention of the author to trace the historical development of the effect of oxygen want on living organisms, since, for the main part, the pertinent discoveries in each field, together with the dates of these discoveries, are given throughout this monograph. It may not be out of place, however, to mention a few of the earliest known observations of the effect of anoxia on man and animals.

Scientific research in oxygen want may be said to have started with the studies of Lavoisier. In 1777 he published his paper *Experiments on the Respiration of Animals and on the Changes Which the Air Undergoes in Passing through the Lungs.* Although oxygen actually was discovered by Priestley, it has been said that he merely isolated it; Lavoisier really discovered it.

Man has subjected himself to anoxic conditions not only by climbing mountains but also by rising to great heights in balloons. Experiments with balloons were made as early as 1783 by the Montgolfier brothers. In 1804 a Frenchman, Robertson, reached an altitude of 26,000 feet in a balloon and was greatly affected by the oxygen want. Gay-Lussac, the distinguished chemist, ascended in a balloon to a height of 23,000 feet and noted only slight effects.

Two of the most famous balloon flights were made in the latter half of the past century. In both instances the balloonists subjected themselves to severe anoxia; and, since these men presumably were unacclimated, it is a marvel that any of them survived the ascent.

Glaisher and Coxwell in 1862 made the highest ascent ever made by balloons up to that time. Glaisher gave an account of this ascent in *Travels in the Air* (9*) and in (10). These men are said to have attained an altitude of 29,000 feet; this seems almost incredible, and Haldane (15) has stated that there is some question whether their aneroid barometer was correct. They experienced strange symptoms, such as disturbances of hearing and vision, paralysis of the legs and arms, and Glaisher finally became unconscious. Coxwell

* Numbers in parentheses refer to bibliographical references on p. 31.

never lost consciousness, but when he attempted to move his arms he found them paralyzed. However, he had the presence of mind to seize the valve rope with his teeth, which started the balloon downward and thus saved their lives.

It was the publication of these experiments and others which attracted the attention of Paul Bert, the brilliant French physiologist, and started him on his studies of the effect of variations of barometric pressure on living organisms.

Perhaps the most famous early balloon ascent, and one which is the most widely known, is that of the balloon "Zenith," in which three scientists—Sivel, Croce-Spinelli, and Tissandier—made a flight on April 15, 1875. Paul Bert, who was so enthusiastically interested in studies in variations of barometric pressure, induced these men to attempt the flight. It had a tragic ending: two of the men died. Tissandier survived and gave a graphic description of the flight in *La Nature* (1875, p. 337) and in Bert's *La Pression barometrique* (p. 1061). Although these men were provided with bags of oxygen, they became so weak after reaching an altitude of 7,500 meters (24,606 feet) that they could not raise their arms to seize the oxygen tube. At a height of 8,000 meters (25,247 feet) Tissandier found it impossible to speak and became unconscious. The instruments showed that the balloon ascended to 28,200 feet and then began to descend of its own accord.

Tissandier related that none of the three men showed signs of violent dyspnea but that the heart beats became very rapid. They experienced great muscular weakness without losing consciousness. Complete unconsciousness developed suddenly without any apparent distress and was preceded by a feeling of sleepiness.

Bert was deeply touched with the disastrous outcome of the flight of the "Zenith," but with characteristic vigor he continued his researches on variations of barometric pressure on the animal organism and in 1878 published his work, *La Pression barometrique*. This work deserves wider reading and greater recognition than it has enjoyed.

Bert performed extensive experiments on animals and men and was the first to show that it was the diminished partial pressure of oxygen which produced the physiologic effects at high altitudes.

Twenty years later the distinguished Italian physiologist Mosso attempted to explain these effects as being due to the loss of carbon dioxide from the body. This was known as the "Acapnia Theory." Mosso's explanation, although rather widely accepted for a time, was found to be untenable, and later work proved that Bert's explanation was the true one.

Since the work of Paul Bert, studies in oxygen want have interested many distinguished physiologists and clinicians as well, and the literature in this field is vast.

DEFINITION OF TERMS

The term *anoxemia* is often used to express the condition of oxygen want in the body. This word is derived from the Greek (*an* [=privation] + *ox*ygen + *emia*) and means a deficient amount of oxygen in the blood; strictly speaking, it should be used only in that sense. There are, however, conditions in which the body suffers from oxygen want that are not caused by a deficiency of oxygen in the blood.

Barcroft (2*) suggested that a general term, *anoxia*, which may be interpreted as "oxygen want," be used to include all conditions of oxygen want in the body, regardless of the cause. He suggested, moreover, that three types of anoxia be recognized: "anoxic," "anemic," and "stagnant." Peters and Van Slyke (28) have suggested a fourth, "histotoxic anoxia" (Gr. *histo* [=tissue] + *toxikon* [=poison]).

The term *anoxia* actually means "without oxygen," and, for this reason, it is not without objection. *Hypoxia* (or *hypoxemia*), which designates a subnormal supply of oxygen, is used by some authors; there is much to be said in its favor, and it is deserving of wider usage. It has been suggested recently by Wiggers (39) that the term *hypoxia* be used when the oxygen in the inspired air is above 12 per cent and that *anoxia* be used when the inspired air contains percentages of oxygen below 12. This somewhat arbitrary division of the state of oxygen want, however, probably will not meet with general favor.

Oxygen lack, too, is an acceptable expression, although it suggests that oxygen may be totally lacking. Less objectionable terms are *oxygen want* and *oxygen deficiency*. They are, of course, general terms and do not specify the cause of the insufficient oxygen supply. Although the term *anoxia* actually signifies a total lack of oxygen, its use is not without parallel in the medical literature, since the word *anemia* is not interpreted to mean that the individual is bloodless. *Anoxia* is doubtless the most convenient term of all, however, since,

* See p. 31 for bibliographical references.

by combining it with the words "anoxic," "anemic," "stagnant," or "histotoxic," the exact type of oxygen deficiency may be expressed.

The word *asphyxia* means "without a pulse" (Gr. *a* [=privation] + *sphyxis* [pulse]), and, strictly speaking, it should not be used synonymously with *anoxia*. It is so firmly established in the literature, however, that it is often used when oxygen deficiency is meant; for example, the anoxia produced by carbon monoxide is frequently spoken of as "carbon monoxide asphyxia." One need not be a purist to regard the term *asphyxia*, used in this sense, as unfortunate.

It is a pity that no clear-cut distinction was made initially in the literature between *anoxia* and *asphyxia*. The definitions given of these two terms in widely used medical dictionaries are not helpful and, in point of fact, add to the confusion.

The author agrees with Gellhorn and Lambert (11) when they state: "It seems important to distinguish sharply between anoxia and asphyxia, because under the clear-cut conditions of physiological experimentations the effects of asphyxia may be fundamentally different from those of anoxia." He is also quite in accord with these authors when they suggest that anoxia should be considered a condition which results from a diminished oxygen supply to the tissues, while the term *asphyxia* should be employed when there is not only an anoxia but also an increased carbon dioxide tension in the blood and the tissues. Used in this sense, asphyxia is often a frequent consequence of anoxia.

Henderson and Haggard (20) have recognized two forms of asphyxia. One form which they described is caused by a cessation of breathing, so that there is an excess of carbon dioxide in the body. This could be caused by anything which stopped respiration, such as mechanical obstruction of the trachea or drugs which paralyze respiration. As the anoxia develops, the carbon dioxide accumulates, so that both conditions affect the body. In the other form which they described, however, there is no interference with breathing except as a terminal event. This type of asphyxia, they explained, could be produced by the inhalation of nitrogen or other inert gas or by deprivation of oxygen. Since there is no interference

with carbon dioxide elimination, anoxia alone exerts a direct action on the body.

In the author's opinion the first form of asphyxia described by these authors should be termed *asphyxia* and the second form *anoxia*.

Recently Henderson (19) has written that "asphyxia involves deficiency of oxygen and generally deficiency of carbon dioxide." It would seem that what he terms asphyxia more nearly approaches anoxia.

The author believes that it is understood by many that in asphyxial conditions there is an accumulation of carbon dioxide in the lungs and in the tissues of the body. If this actually is the concept that many biologists have of asphyxia, it is not difficult to accept the distinction between anoxia and asphyxia previously mentioned; that is, anoxia designates a diminished supply of oxygen to the tissues, and asphyxia a condition of anoxia combined with an increase of carbon dioxide tension in the blood and in the tissues. If this distinction were generally accepted, it would do away with much misconception and would distinguish sharply between asphyxia and anoxia.

CLASSIFICATION OF ANOXIA

According to the previously mentioned suggestions of Barcroft and of Peters and Van Slyke, four types of anoxia are recognized:

1. *Anoxic anoxia* (*anoxemia*).—In this type there is a lack of oxygen in the arterial blood. The tension in the arterial blood is low; and the hemoglobin, therefore, is not saturated with oxygen to its normal extent.

2. *Anemic anoxia.*—The arterial blood contains oxygen at a normal tension, but there is a shortage of functioning hemoglobin.

3. *Stagnant anoxia.*—Here, although the arterial blood has a normal amount of oxygen held under normal tension, it is not given off to the tissues in sufficient quantities.

4. *Histotoxic anoxia.*—As the term suggests, the tissue cells are poisoned and, therefore, unable to make proper use of the oxygen.

ANOXIC ANOXIA

This type affects the whole body and is one of the most serious forms of anoxia. It is produced characteristically by high altitudes, although it may be brought about by any process which interferes with the oxygen passing into the blood. It may be produced by the following conditions:

1. Low tension of oxygen in inspired air
   - *a*) High altitudes
   - *b*) Breathing inert gases
   - *c*) Anesthetic agents
2. Abnormal conditions within the lungs
   - *a*) Fluid (caused by drowning) or from edema or exudates
   - *b*) Obstruction of air passages by other than fluids
   - *c*) Pneumonia
   - *d*) Collapse of lung
   - *e*) Emphysema
3. Shallow respiratory movements from any cause
4. Reflex inhibition of respiration from any cause (exposure to nonrespirable gases, blow on solar plexus, etc.)
5. Embryological malformations of the heart or blood vessels

In order to understand clearly the cause of anoxia produced by low oxygen tensions in the inspired air, it is well to recall what happens under normal conditions. At normal atmospheric pressure of 760 mm. Hg, oxygen exerts a partial pressure of 159 mm. Hg. At this partial pressure of oxygen the hemoglobin in the arterial blood is 95 per cent saturated with oxygen, or, expressed in another way, it contains 19 volumes per cent. (Full saturation would be equal to 20 volumes per cent.) As the blood passes through the capillary bed, approximately 5 volumes per cent of oxygen are removed, so that the mixed venous blood contains 14 volumes per cent, or a hemoglobin saturation of 70 per cent. The dissociation curve of oxyhemoglobin (Fig. 1) shows that 70 per cent oxygen saturation corresponds, roughly, to a pressure of 40 mm. Hg. The oxygen, therefore, is carried to the tissues at a relatively high pressure, so that there is a high pressure gradient between the blood capillaries and the tissues.

During anoxic anoxia the partial pressure of oxygen and saturation of hemoglobin are both reduced, depending, of course, upon the severity of the anoxia. As a consequence, the high pressure gradient between the blood in the capillaries and tissues is reduced, so that it becomes much less effective in supplying oxygen to the tissues.

It is recognized now, moreover, that the reduction in the partial pressure of oxygen in the arterial blood is more important than is the lack of oxygen saturation. Evidence is also available that the velocity of oxidative processes in the tissues is proportional to the partial pressure which the oxygen exerts. The lowering, then, of the partial pressure of oxygen in inspired air is, indeed, a serious handicap to the body.

Finally, the increased respirations produced by anoxia wash the carbon dioxide out of the lungs, and as a consequence the carbon dioxide arterial pressure falls. It is known that one of the important factors in the dissociation of oxygen from oxyhemoglobin is the carbon dioxide tension in the arterial blood (Fig. 2). Since, during anoxic anoxia the carbon dioxide tension is decreased, the hemoglobin does not give up its oxygen readily, and as a consequence the tissues suffer from oxygen want, although there may be adequate oxygen in the

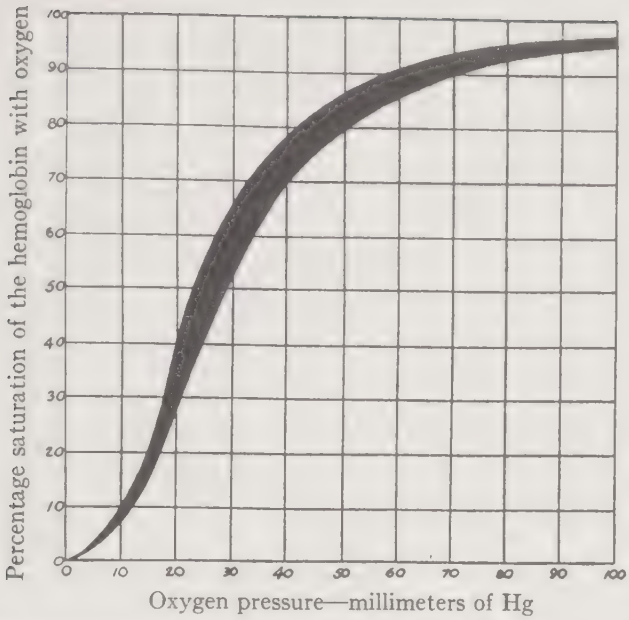

FIG. 1.—The dissociation curve of oxyhemoglobin for human blood. (From Barcroft, *The Respiratory Function of the Blood* [Cambridge University Press, 1914], p. 226.)

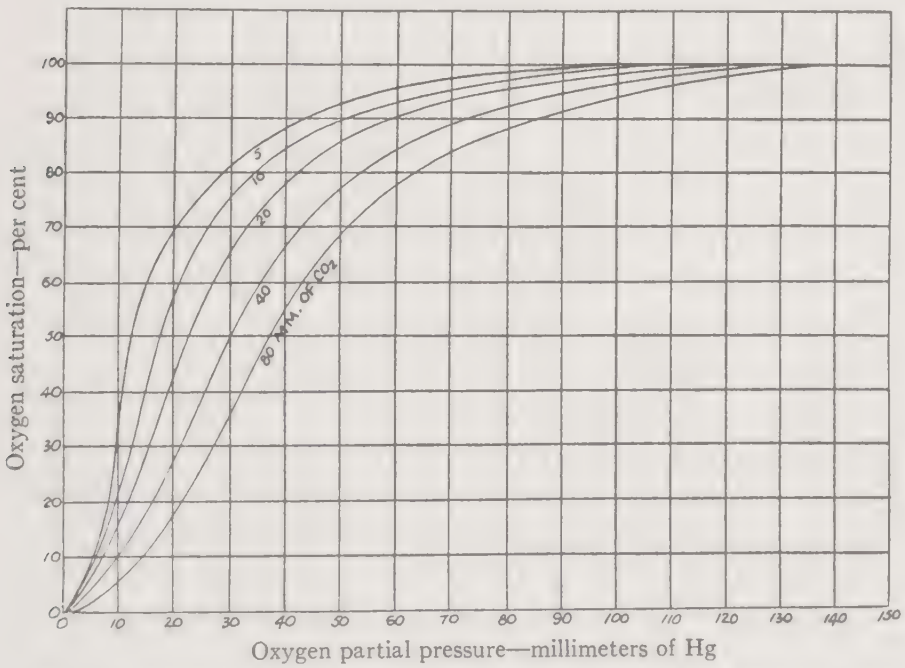

FIG. 2.—Curves of dissociation of the oxyhemoglobin at different pressures of carbon dioxide. Several curves are shown to indicate that the tension of carbon dioxide greatly influences the dissociation of the oxyhemoglobin. (After Bohr.)

blood. As has been pointed out by Wright (40*), the tissues in this type of anoxia are hampered in three ways: (1) the rate of oxidation is diminished because of the low tension in the blood; (2) there is less oxygen in the blood than normally; and (3) the low carbon dioxide tension hampers the dissociation of oxyhemoglobin.

ANEMIC ANOXIA

This type is, on the whole, less serious than the anoxic type of anoxia; however, it does affect the whole body. The hemoglobin which is present in the arterial blood is normally saturated with oxygen, and the oxygen tension in the blood is normal; there is then no interference with tissue oxidation. The cause of the anoxia is a reduction in the volume of oxygen which can be furnished to the tissues. In less severe conditions, as long as the subject remains at rest, the body does not suffer from oxygen want; there are no reserves of oxygen in the blood, however, so the subject's ability to do work is greatly decreased.

The anemic type of anoxia may be caused by the following conditions:

1. Hemorrhage from any cause
   a) Acute
   b) Chronic
2. Anemia
   a) Primary—pernicious anemia
   b) Secondary—chlorosis
3. Alterations in hemoglobin
   a) Nitrites
   b) Chlorates
   c) Coal-tar derivatives
4. Carbon monoxide poisoning

STAGNANT ANOXIA

In the stagnant type of anoxia, which is due to a diminution in circulatory rate, only local areas of the body may be affected, or the whole body may be involved. The blood is normally saturated with oxygen; and the oxygen load, as well as the tension under which it is held, also may be normal. Anoxia is produced because the amount of oxygen reaching the tissues is not adequate; the slow circulation allows the blood time to give up a larger percentage of its oxygen. The slow circulation also allows the accumulation of carbon dioxide in the tissues, which facilitates the dissociation of oxygen from the hemoglobin; the oxygen then may be delivered under low pressure.

* See p. 31 for bibliographical references.

Any measure, of course, which improves the circulation will alleviate the anoxic state.

The stagnant type of anoxia may be produced by the following:

1. Failure of the circulation
   a) General
   b) Local—Raynaud's disease, etc.
2. Impairment of venous return
3. Shock

HISTOTOXIC ANOXIA

In this type of anoxia the cells are not able to utilize the oxygen, although the amount of oxygen in the blood may be quite normal and under normal tension. It is characteristically produced by

TABLE 1*

Type of Anoxia	O_2 Capacity of Blood (Vol. Per Cent)	Arterial Blood: O_2 Content (Vol. Per Cent)	Arterial Blood: Proportion of Hb Oxygenated at pH_8 7.42 (Per Cent)	Arterial Blood: O_2 Tension (Mm.)	O_2 Lost by Blood in Perfusing the Tissues (Vol. Per Cent)	Venous Blood: O_2 Content (Vol. Per Cent)	Venous Blood: Proportion of Hb Oxygenated (Per Cent)	Venous Blood: O_2 Tension at pH_8 7.39 (Mm.)
None, normal	20.0	19.0	95	80	4.2	14.8	74	41
Anoxic	20.0	14.8	74	*43*	4.2	10.6	53	28
Anemic anemia	*10.0*	9.5	95	80	4.2	5.3	53	28
Anemic CO poisoning†	*15.3*†	14.7	74	80	4.2	10.1	50	28
Stagnant	20.0	19.0	95	80	*8.4*	10.6	53	28

* The table illustrates the manner in which the various types of anoxia may produce the same lowered oxygen tension in the venous blood and presumably in the tissues. The figures in italics indicate the causes of the anoxia. (From Peters and Van Slyke, *Quantitative Clinical Chemistry* [Baltimore: Williams & Wilkins Co., 1932], I, 584.)

† The remainder of the hemoglobin is combined with CO.

cyanides. It may be produced, however, theoretically by any agent which depresses cellular respiration.

The mechanism of the action of histotoxic anoxia is closely associated with the question of cellular oxidation. Since space does not permit an exhaustive consideration of this topic here, the reader is referred to the original investigations of Warburg (35, 36, 37) and those of Keilin (23), whose brilliant researches have thrown so much light on problems of cellular oxidation.

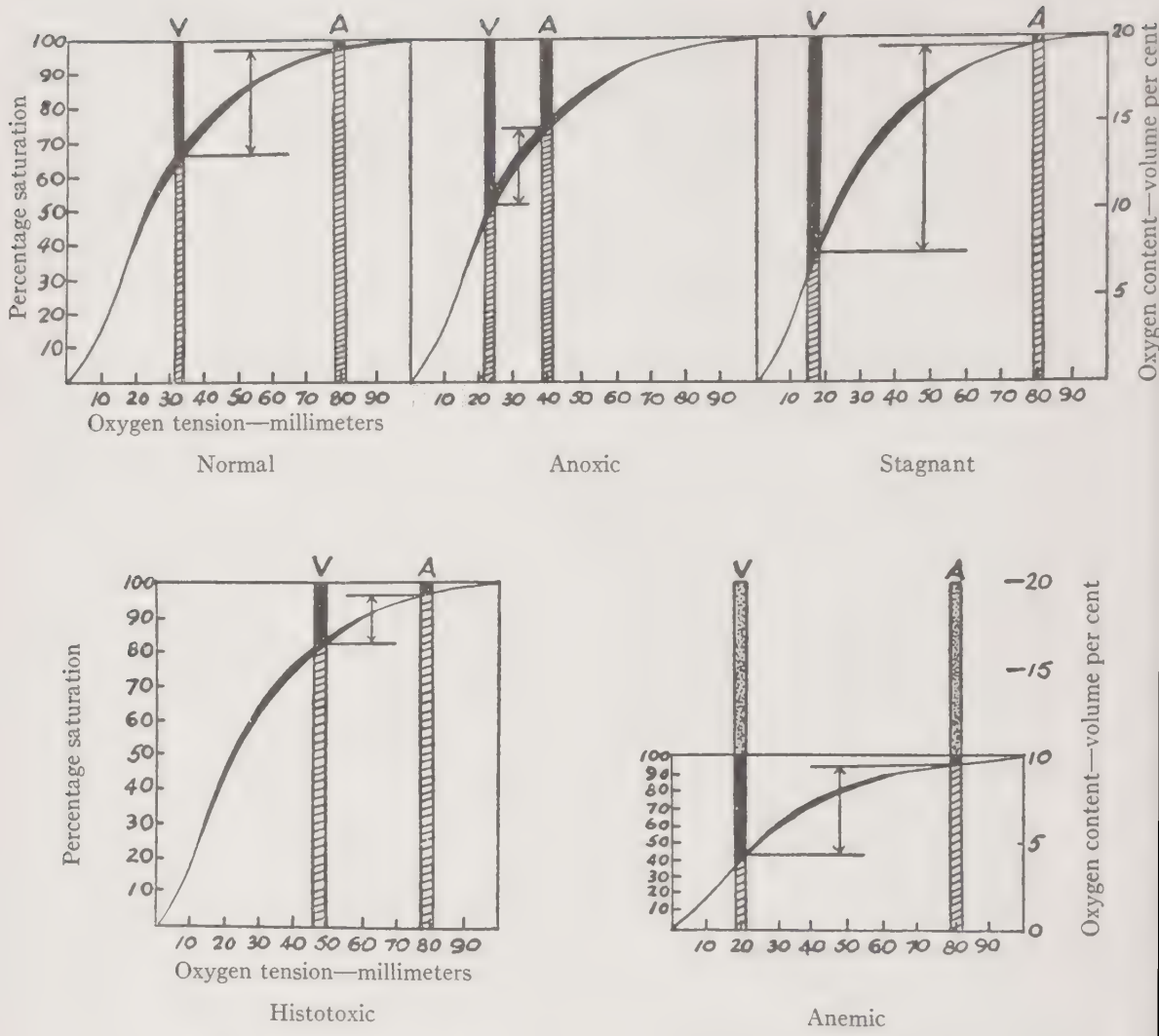

FIG. 3.—Diagram illustrating types of anoxia. Columns representing arterial blood (*A*) and venous blood (*V*) are superimposed upon the dissociation curve. The black portion of column represents reduced hemoglobin; shaded portion, oxygenated hemoglobin. Dotted portion of column in the case of anemic anoxia represents the hemoglobin that is lost by hemorrhage or unfit for oxygen transportation, as in carbon monoxide poisoning. The perpendicular arrows denote the volume of oxygen delivered to the tissues from a unit of blood. (From Means, *Dyspnea* [Baltimore: Williams & Wilkins Co., 1924], p. 67, with additions from Best and Taylor, *Physiological Basis of Medical Practice* [Baltimore: Williams & Wilkins Co., 1939], p. 574.)

It is thought that, normally, a combination of respiratory enzyme (Warburg's *Atmungsferment*) and cytochrome constitutes the essential oxidizing systems of cells. Schematically it may be represented:

Molecular oxygen → Oxidase (Warburg's *Atmungsferment*) → Cytochrome

It is thought that Warburg's oxidase acts as a catalyzing agent. It has been shown by Warburg that cyanides act by inactivating the iron-containing catalyst. Keilin has demonstrated that the following compounds all interfere with the ability of cytochrome to take up and release oxygen: cyanides, narcotics, alcohol, formaldehyde, acetone, and ethyl urethane. This does not mean, of course, that there may not be other compounds capable of doing the same thing. From his work he concluded that, while cyanide inactivates the cytochrome by preventing its combining with oxygen, the narcotics act differently in that they do not prevent the formation of oxycytochrome but cause it to hold the oxygen so tenaciously that it is not available for cellular oxidation.

THE QUESTION OF HISTOTOXIC ACTION OF CARBON MONOXIDE

It is generally believed that carbon monoxide acts by preventing the normal carriage of oxygen in the blood and not as a direct tissue poison (14, 16). Moreover, according to Killick (24), the percentage saturation of the blood with carbon monoxide represents fairly accurately the degree of anoxia.

Carbon monoxide, however, is capable of exerting a histotoxic action, since the oxidative enzymes of tissues may be inhibited; but this is thought to be evident only at relatively high partial pressure of the gas. It was reported by Warburg (37), in 1926, that the respiration of yeast was inhibited in a mixture of carbon monoxide with oxygen, but this inhibition was evident only when the partial pressure of the carbon monoxide was nearly five times as high as that of oxygen. That carbon monoxide arrests tissue oxidation by uniting with the iron of a catalyst has been suggested by Warburg (38).

In 1927 J. B. S. Haldane (13), working with rats and using high partial pressures of carbon monoxide, concluded that some sub-

stance in the tissue was affected. De Meio *et al.* (5) in 1934 studied the problem further by comparing the metabolism of isolated tissues in mixtures of oxygen and carbon monoxide with nitrogen and reported that certain tissues showed inhibition with carbon monoxide.

Proof offered that carbon monoxide does not act as a histotoxic agent is that animals without hemoglobin, such as the cockroach, show indifference to carbon monoxide (14). This may be, however, because the degree of affinity of iron-porphyrins for carbon monoxide varies greatly. It is also claimed that cultures of chick neuroblastic tissues are unaffected by carbon monoxide (12). It should be borne in mind, of course, that the adult type of cell may be affected differently by carbon monoxide than are embryonic cells.

Recently Maurer (27) reported the effects of anoxic anoxia and anoxia produced by carbon monoxide on the flow of lymph. He obtained very comparable results with both methods and suggested, therefore, that this confirmed the belief that carbon monoxide of itself was nontoxic and acted only through its ability to reduce the oxygen-carrying capacity of the blood.

In summary, it may be said that, although carbon monoxide acts principally by preventing the normal carriage of oxygen, some authors feel that it may also interfere, in a measure, with tissue oxidation. It is obvious that further research is needed on this important problem.

ACUTE AND CHRONIC ANOXIA

Besides classifying anoxia into the four different types, it is also customary to make a distinction between acute and chronic anoxia. Dr. Carl F. Schmidt in *Macleod's Physiology in Modern Medicine* (29) very appropriately suggests that to these be added what he terms "fulminating anoxia."

Fulminating anoxia.—This is a very rapidly induced type of anoxia, such as may be caused by inhalation of undiluted physiologically inert gases, such as nitrogen, methane, or helium. A mammal subjected to these gases will become unconscious in about 45–90 seconds and, unless oxygen is given, will collapse. Fulminating anoxia can be produced also by blocking the trachea. This type of anoxia resembles asphyxia, but the term should not be used synonymously with anoxia.

This type of anoxia may be produced unwittingly by administering nitrous oxide anesthesia and not simultaneously giving sufficient oxygen. It is encountered also in mines which contain a high content of methane gas or in other places which have vitiated air, such as old wells, holds of ships, or other closed spaces which have been fumigated with poisonous vapors without subsequent proper ventilation.

Acute anoxia.—The distinction between acute anoxia and that of fulminating anoxia is that the degree of anoxia is not so severe and that the symptoms produced develop less rapidly. Experimentally, acute anoxia may be produced (1) by placing the subject in a low-pressure chamber from which air may be withdrawn; (2) by the use of a rebreather apparatus; or (3) by allowing the subject to breathe a gas mixture diluted by some inert gas.

In everyday life, aviators, people who live at high altitudes, mountain-climbers, and balloonists may all be affected by acute anoxia. Acute anoxia may be produced also by carbon monoxide gas and by certain diseases of the heart, blood, circulation, or lungs.

The symptoms which acute anoxia may cause are: shortness of breath, palpitation, headache, nausea, vomiting, mental confusion, muscular weakness and inco-ordination, cyanosis, and sometimes disturbances in vision and hearing. Owing to the symptoms which acute anoxia may present, it has been suggested by Barcroft (2) that acute anoxia resembles alcoholic intoxication.

Acute anoxia, such as is commonly produced by carbon monoxide, may prove rapidly fatal, since unconsciousness develops early without much, if any, warning or respiratory distress. This is the reason people often lose their lives when cars are left running in closed garages; unconsciousness develops so insidiously and painlessly that they are unaware of any danger.

While presumably all the organs of the body are affected by acute anoxia, the central nervous system and the respiratory and circulatory systems appear to be affected the most. The details of the nature of the effect of acute anoxia on these various organs will be considered later. Mountain sickness, which is produced by acute anoxia, will also be considered later.

Chronic anoxia.—The symptoms associated with chronic anoxia are produced by long sojourns at high altitudes or by repeated exposures to subnormal supplies of oxygen. Barcroft (2) has suggested that the symptoms produced by chronic anoxia resemble fatigue, both mental and physical. To avoid reiteration the mental symptoms will not be discussed here but will be considered in the section which deals with anoxia and the central nervous system.

The physical symptoms may be mentioned briefly. Even in the acclimatized individual, there is at high altitudes a dyspnea on exertion, so that the ability to do hard physical labor is not what it is at sea-level. Physically, men tire easily at high altitudes, and it is often difficult for them to do a good day's work. Recovery from fatigue, furthermore, is much slower than it normally is at lower altitudes. At extremely high altitudes, such as encountered in climbing high mountain peaks, physical work is very difficult, so that it may be necessary to rest virtually between each step upward. It has been said that at these extreme altitudes the mountaineer thinks twice before he turns over in bed.

A chronic mountain sickness may develop after a long sojourn at high altitudes; this will be considered, however, when mountain sickness is discussed. Chronic anoxia may also produce degenerative changes in certain organs.

EXPRESSION OF THE DEGREE OF ANOXIA

PERCENTAGE OF OXYGEN

In expressing the degree of anoxia the term *oxygen percentage* is often used. This is permissible if it is used to express the actual amount of oxygen present in a known mixture—for instance, a mixture containing oxygen diluted with nitrogen. It must be remem-

TABLE 2

RELATION OF ALTITUDE, PRESSURE, AND OXYGEN*

Mm. Hg	Elevation (Feet)	O_2 (Per Cent)	Mm. Hg	Elevation (Feet)	O_2 (Per Cent)
760	0	20.96	412	16,000	11.39
732	1,000	20.15	397	17,000	10.97
704	2,000	19.38	382	18,000	10.56
677	3,000	18.64	368	19,000	10.16
651	4,000	17.93	354	20,000	9.78
626	5,000	17.25	341	21,000	9.41
602	6,000	16.60	328	22,000	9.05
579	7,000	15.97	315	23,000	8.70
557	8,000	15.37	303	24,000	8.35
536	9,000	14.80	290	25,000	8.01
516	10,000	14.25	278	26,000	7.68
497	11,000	13.73	266	27,000	7.35
478	12,000	13.23	254	28,000	7.03
461	13,000	12.75	242	29,000	6.71
444	14,000	12.28	230	30,000	6.40
428	15,000	11.83			

* From *Air Service Medical* (Washington, D.C.: U.S. Printing Office, 1919), p. 166.

bered, however, that altitude does not affect the percentage composition of oxygen of the atmosphere; this has been shown to be true to at least a height of 72,000 feet (Steven [33*]). It is not, then, the oxygen percentage which changes in rare atmosphere but rather the partial pressure the oxygen exerts.

Percentages of oxygen, however, have been translated into altitudes, as shown in Table 2. Such a table may produce considerable confusion, since, as just mentioned, the percentage composition of oxygen of the air does not change with altitude. It will be seen in the

* See p. 31 for bibliographical references.

table, for example, that 10.56 per cent of oxygen is equivalent to an altitude of 18,000 feet. What this actually means is that this percentage of oxygen in a gas mixture at sea-level exerts the same partial pressure that oxygen does at an altitude of 18,000 feet. It also means 10.56 per cent of an atmosphere pressure. If this is clearly understood, confusion will be avoided.

THE PARTIAL PRESSURE OF OXYGEN

According to the mechanical theory of gas pressure, as now understood, each gaseous constituent of the air is capable of exerting its own partial pressure corresponding to the proportion of that gas present. The partial pressure of all gases decreases with altitude; that is, the higher the altitude, the less partial pressure each gas exerts. The degree of anoxia, therefore, may be expressed by stating the partial pressure of oxygen in millimeters of mercury. The percentage of oxygen at sea-level is 20.96, and the barometric pressure is 760 mm. Hg; so the partial pressure exerted by the oxygen at sea-level would be $760 \times 0.2096 = 159$ mm. Hg. Similarly, the barometric pressure at 18,000 feet is approximately 380 mm. Hg; therefore the partial pressure of oxygen would be $380 \times 0.2096 = 80$ mm. Hg. It is clear, then, that there is a direct ratio between barometric pressure and partial pressure of oxygen.

BAROMETRIC PRESSURE

Since air has mass, the higher the altitude, the shorter the column of Hg the air will support. The degree of anoxia may also then be expressed by giving the height of the mercury column, that is, the barometric pressure. A relationship exists between the altitude and barometric pressure, but this relationship is not a straight line. Figure 4 shows that there is progressively less drop in pressure as the altitude becomes higher; that is, the relation is logarithmic. Table 2 also shows the altitude-pressure relationship.

APPROXIMATE ALTITUDES OF WELL-KNOWN REGIONS

While it is more accurate and less confusing to express the degree of anoxia in partial pressures of oxygen in millimeters of mercury or by giving the actual barometric pressure, it is helpful to give the approximate altitude in feet corresponding to these pressures. This

often orients the reader and allows him, if he is so minded, to make certain comparisons and interpolations which otherwise he might not be able to do.

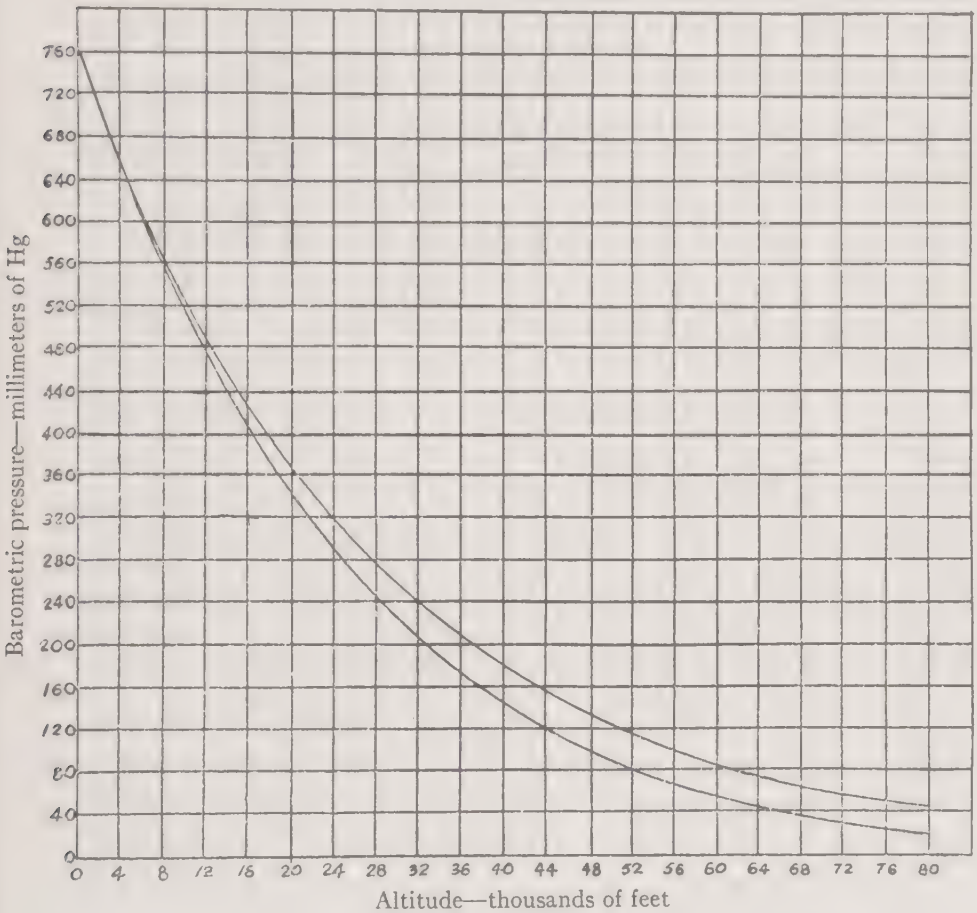

FIG. 4.—Curves showing relation of barometric pressure to height. The upper curve is calculated from the formula given by Zuntz, Loewy, Muller, and Caspari, assuming a mean temperature of 15° C. The lower curve is calculated according to the I.C.A.N. conventional law, assuming standard conditions. (From Armstrong, *Principles and Practice of Aviation Medicine* [Baltimore: Williams & Wilkins Co., 1939], p. 250.)

It is common knowledge, for example, that the city of Denver, Colorado, is situated at an altitude of about 5,000 feet and that much of the plateau region of southwestern United States lies at an altitude between 5,000 and 7,000 feet. It is rather generally known, too, that the altitude of the summit of Pike's Peak is about 14,000 feet

(14,100 feet). Many readers are familiar also with the altitude of Mount Everest, presumably the highest peak in the world, approxi-

TABLE 3

ALTITUDE-PRESSURE TABLE BASED ON THE UNITED STATES STANDARD ATMOSPHERE-FEET-MILLIMETERS*

Altitude (Feet)	Pressure (Mm. Hg)	Altitude (Feet)	Pressure (Mm. Hg)	Altitude (Feet)	Pressure (Mm. Hg)	Altitude (Feet)	Pressure (Mm. Hg)
0....	760.0	21,000....	334.8	42,000....	127.9	63,000....	46.9
1,000....	733.0	22,000....	320.8	43,000....	122.0	64,000....	44.7
2,000....	706.6	23,000....	307.4	44,000....	116.3	65,000....	42.6
3,000....	681.0	24,000....	294.4	45,000....	110.9	66,000....	40.7
4,000....	656.4	25,000....	282.0	46,000....	105.7	67,000....	39.8
5,000....	632.4	26,000....	269.8	47,000....	100.8	68,000....	37.0
6,000....	609.0	27,000....	258.2	48,000....	96.0	69,000....	35.2
7,000....	586.4	28,000....	246.8	49,000....	91.6	70,000....	33.6
8,000....	564.4	29,000....	236.0	50,000....	87.3	71,000....	32.0
9,000....	543.2	30,000....	225.6	51,000....	83.2	72,000....	30.5
10,000....	522.6	31,000....	215.4	52,000....	79.3	73,000....	29.1
11,000....	502.6	32,000....	205.8	53,000....	75.6	74,000....	27.7
12,000....	483.2	33,000....	196.4	54,000....	72.1	75,000....	26.5
13,000....	464.6	34,000....	187.4	55,000....	68.8	76,000....	25.2
14,000....	446.4	35,000....	178.7	56,000....	65.5	77,000....	24.0
15,000....	428.8	36,000....	170.4	57,000....	62.5	78,000....	22.9
16,000....	411.8	37,000....	162.4	58,000....	59.6	79,000....	21.9
17,000....	395.4	38,000....	154.9	59,000....	56.8	80,000....	20.8
18,000....	379.4	39,000....	147.6	60,000....	54.1		
19,000....	364.0	40,000....	140.7	61,000....	51.6		
20,000....	349.2	41,000....	134.2	62,000....	49.2		

* From Armstrong, *Principles and Practice of Aviation Medicine* (Baltimore: Williams & Wilkins Co., 1939), p. 249.

mately 29,000 feet. And, finally, those who are air-minded are doubtless familiar with the height at which transcontinental planes often fly, namely, about 12,000 feet.

EXPERIMENTAL METHODS OF PRODUCING ANOXIA

Although Paul Bert (4*) in 1878 showed that it was the lowered partial pressure of oxygen in the air which produced the physiologic responses at high altitude, some investigators felt that the low barometric pressure might also be responsible for some of the effects. It has been shown, however, by several workers (2, 4, 18, 26, 30) that the reactions characteristic of high altitude can be produced by subjecting the animal organism to a deficiency of oxygen. Lutz and Schneider (26) made quite extensive experiments and produced anoxic anoxia several different ways; they came to the conclusion that the physiologic responses obtained were quite comparable.

While the latter is doubtless true, several authors have called attention to certain quantitative differences in results obtained when different methods of producing anoxia are used. It has been suggested (22, 32) that the acute anoxia produced with the rebreathing apparatus is not entirely comparable to the changes experienced at high altitudes; significant differences in the circulation and in the aftereffects and even other differences are said to occur.

Haldane and Priestley (17) have stated that anoxemia is more effectively produced by lowering the percentage of oxygen in the air breathed at normal atmospheric pressure than by producing it by lowering the partial pressure of oxygen, that is, by causing a diminution of total barometric pressure. They have pointed out (17, chap. x) that the rate of diffusion in a gas increases with a fall of barometric pressure, because the mean free path of each molecule, before it strikes another, is increased. This makes it possible for the oxygen molecule in the vicinity of the alveolar epithelium to reach it more rapidly, and the fall in alveolar oxygen pressure at low barometric pressures is thus partly compensated.

EXPERIMENTAL METHODS OF PRODUCING ANOXIC ANOXIA

This type of anoxia may be produced by five different methods: (1) use of a rebreather; (2) use of a low-pressure chamber; (3) dilu-

* See p. 31 for bibliographical references.

tion of air or oxygen by some inert gas, such as nitrogen or helium; (4) artificial pneumothorax; and (5) artificial restriction of free influx of atmospheric air into the lungs.

I. THE REBREATHER

The principle of the rebreather apparatus is shown diagrammatically in Figure 5. The apparatus consists merely of a bag which may be filled with air and an absorbing can of caustic soda placed between the bag and the mouthpiece.

A clip is placed on the subject's nose, and he is allowed to breathe into and out of the bag. The oxygen is used, of course, by the body;

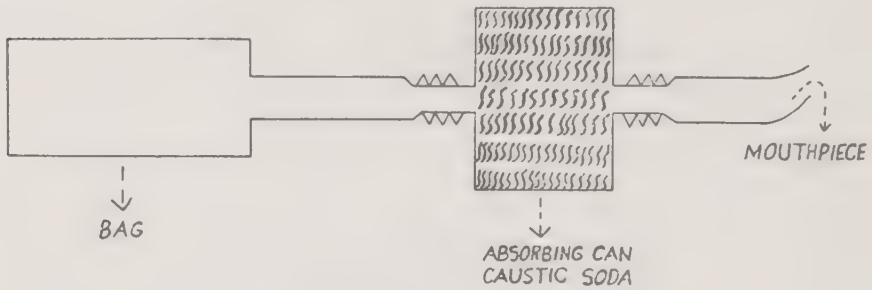

FIG. 5.—Simple form of rebreathing apparatus. (From *Air Service Medical* [Washington, D.C.: U.S. Government Printing Office, 1919], p. 342.)

and, as the carbon dioxide is removed by the caustic soda, the volume of air in the bag steadily decreases and the percentage of oxygen grows progressively less. If the capacity of the bag is about 60 liters of air, the subject will reduce the oxygen to 7 per cent in about 30 minutes. Roughly, this is equivalent to an altitude of 28,000 feet—a severe degree of anoxia.

a) *The Flack bag method* (*8*).—The apparatus consists of a bag containing about 5 liters of room air. The subject (with a clip on his nose) breathes in and out of the bag. The carbon dioxide is removed by a cylinder containing a proper absorbent, which is placed between the bag and the mouthpiece. The arrangement is ostensibly like that shown in Figure 5. The subject breathes out of the bag until the oxygen content is so reduced that he is forced to discontinue breathing; the length of time is noted, and the air in the bag is analyzed for oxygen content.

b) *The Henderson-Pierce rebreather.*—A more elaborate rebreather is that described by Henderson and Pierce (21), which is diagrammatically shown in Figure 6.

The steel tank (*T*) represents the base of the instrument, which may hold from 60 to 80 liters of air. Air is inspired from the tank

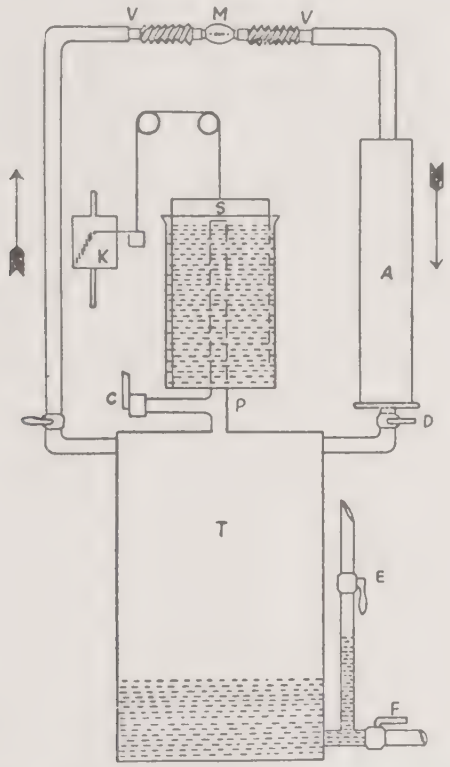

FIG. 6.—Henderson-Pierce rebreather. (From *Air Service Medical* [Washington, D.C.: U.S. Government Printing Office, 1919], p. 344.) For description see text.

through valve *E* and expired through the pipe to cartridge *A*. The flutter-type valves (*v* and *V*) keep the air stream flowing in the proper direction. The wet spirometer (*S*), which is carefully counterbalanced and which rests on the tank (*T*), communicating with its interior through the pipe (*P*), maintains the contained air at approximate atmospheric pressure by allowing a change in volume. The movements of the spirometer are properly recorded upon the smoked drum of the kymograph (*K*). In order to replace the volume of used oxygen and to flush out the tank after an experiment, water

may be admitted through valve *E*. The tank (*T*) may be drained through valve *F*. The rebreathed air may be flushed from the tank with atmospheric air by opening valve *C*. While flushing the tank (*T*) with water, valve *D* should be kept closed, so that water will not enter cartridge *A*. This cartridge, which removes the carbon dioxide from the expired air, consists of a cylindrical paper tube filled with solid caustic soda, which is cast in shells so as to expose a large surface to the air. To prepare it for use in the machine, $\frac{1}{4}$-inch holes are pierced in the ends with a pencil. A brass ring is inserted into the lower end of the cartridge; a rubber ring is fitted over the end; and the whole inserted into the absorption cylinder.

2. THE LOW-PRESSURE CHAMBER

Various types of low-pressure chambers have been described in the literature (1, 3). The simplest means of operating such a chamber is to withdraw the air by means of a suitable air pump. At the opposite end of the tank from which the air is withdrawn, fresh air should be allowed to enter. In order to produce a low pressure within the chamber, the air can be withdrawn faster than it is allowed to enter. Any degree of pressure within the chamber may be produced by manipulating the intake valve.

There is an elaborate low-pressure chamber at the Wright Flying Field, at Dayton, Ohio; there is one also at Randolph Flying Field in Texas. During the World War (1917–19) a fully equipped low-pressure chamber was constructed (which later was dismantled) at the Medical Research Laboratory of the Air Service, Mineola, Long Island.

Low-pressure chambers may be made sufficiently large to accommodate a bed, table, and chair and may have electric lights and other conveniences so that individuals may live in them reasonably comfortably for several days. Some chambers are arranged so that the temperature and humidity may be controlled.

The chamber at Mineola contained several windows, so that the experiments could be watched from without. An oxygen supply was piped through the wall into the chamber to a distributing board, arranged so as to supply an individual tube and mouthpiece for each subject. The operator, who sat on the outside, could observe

those inside as well as communicate with them by telephone. He could observe also the mercury manometer indicating the barometric pressure within the chamber, expressed in millimeters of mercury and in feet above sea-level. From the same position he could regulate the oxygen supply, control the flow of air through the chamber, and operate the switch for the motor. Thus, all operations could be carried out without the operator leaving his post.

These elaborate low-pressure chambers are not necessary for the usual routine experiments on anoxia, especially where animals are used. For several years the author (34) has used a relatively inexpensive low-pressure chamber which can accommodate two or three people or several large dogs. Such a chamber must be constructed of sufficiently heavy material to withstand atmospheric pressure when the air is withdrawn. The one in question is made of 5.0-mm. boiler-plate steel with the seams oxyacetylene welded. The windows are made of 12-mm. plate glass, mounted in heavy cast-iron frames. Its construction is not difficult, and it can be made in any reasonably well-equipped welding-shop.

Small, inexpensive low-pressure chambers for animal experimentation have been described by Kolls and Loevenhart (25).

3. DILUTION OF AIR OR OXYGEN BY NITROGEN

a) *The Dreyer method* (7).—One of the well-known methods which uses the principle of air dilution. The apparatus is arranged so that the air which the subject breathes is steadily increasing in percentage of nitrogen. Lutz and Schneider (26) have used this method, the air being delivered to the subject by means of an American model of a Tissot gas mask.

b) *The Douglas breathing bag* (6).—This well-known piece of apparatus is often used to produce anoxic anoxia. The bag is made of rubber covered with canvas; the usual capacity is 100 liters of gas, but bags of larger capacity may be used. By running compressed air or nitrogen through a gas meter the oxygen concentration can be set at any desired level.

c) *Dilution of air or oxygen with an apparatus for administering anesthesia.*—The author has employed a simple method for diluting oxygen with nitrogen, which is especially useful for animal experi-

mentation. An apparatus with which nitrous oxide or ethylene anesthesia ordinarily is administered is used. Oxygen is diluted with nitrogen, and the mixture is allowed to flow in an appropriate bag, which, in turn, is led to the animal. Either the bag may be connected directly with the trachea, or it may be connected with a suitable mask which fits over the muzzle of the animal. The animal then breathes out of the bag, and a flutter valve is arranged so that the animal exhales to the outside, thus preventing the accumulation of carbon dioxide. The pressure under which the gases are delivered into the bag may be controlled by a suitable valve. The accuracy of this apparatus varies from $\frac{1}{2}$ to 1 per cent. It is especially useful when a low-pressure chamber is not available and also for experiments which, for one reason or another, cannot be performed in a low-pressure chamber.

d) Dilution of air in respiratory chamber with nitrogen.—Obviously, if it is desired, the air in a respiratory chamber can be diluted with a given quantity of nitrogen. This method of producing anoxia, however, has been used by comparatively few workers.

4. PRODUCTION OF ARTIFICIAL PNEUMOTHORAX TO PRODUCE ANOXIA

Anoxia is occasionally produced experimentally by the establishment of an artificial pneumothorax. Pneumothorax cannot be employed with success in dogs, for in these animals there is imperfect separation of the two halves of the thoracic cavity. The cat and the rabbit, however, lend themselves to this type of experiment. It has been observed that after the production of artificial pneumothorax the body adapts itself to this condition much as it does to high altitudes. This method of producing anoxia has been criticized, since anatomical abnormalities in the body are caused by the collapse of one lung.

5. ARTIFICIAL RESTRICTION OF FREE INFLUX OF ATMOSPHERIC AIR INTO THE LUNGS

There are a few reports in the literature where restriction of free influx of atmospheric air was employed to produce anoxia. In order to bring this about, the trachea may be compressed to the desired diameter by means of a wire.

APPRAISAL OF DIFFERENT METHODS OF PRODUCING EXPERIMENTAL ANOXIC ANOXIA

It seems in order to present briefly a critical appraisal of the different methods of producing experimental anoxic anoxia. The method of choice depends largely upon the nature of the experiment. If it is desirable not to hamper the activities of the subject, the use of the Douglas bag to produce anoxia is the most satisfactory method. This well-known piece of apparatus is relatively inexpensive, compared with a low-pressure chamber; and, further, it takes up but little storage space. It might be pointed out that wearing a mask produces an unphysiologic condition, but most subjects seem not to mind the slight inconvenience it causes.

Any method which makes use of the rebreather for inducing anoxia may be criticized on the ground that the subject is not exposed to a diminished air pressure. This same criticism applies if the subject is allowed to inhale air or oxygen diluted with some inert gas under normal atmospheric pressure. It will be recalled that some investigators feel that anoxia produced without changing the atmospheric pressure is not entirely comparable to the changes experienced at high altitudes (p. 21).

In view of the last-named criticism and for other reasons as well, probably the most satisfactory method of producing anoxic anoxia experimentally is by the use of the low-pressure chamber. If such a chamber is properly constructed, the subject can make himself comfortable and can be observed constantly by the operator.

In working with human beings the psychic factor must be considered. Reliable data cannot be obtained if the subject is apprehensive. The subject should be made to understand that every precaution has been taken to insure his safety. Valves should be installed which open automatically if the pressure falls too low, and a valve which can be controlled within the chamber by the subject in case of an emergency provides a further sense of security. The installation of these safety devices, however, should not make the operator feel that his responsibility is lessened; the subject should be under constant surveillance.

The psychic factor is not so important when working with animals, although it should be borne in mind that, in order to secure

trustworthy results, as normal a physiologic state as the experiment permits should be maintained.

Some experimental methods of producing anoxia, as previously mentioned, are unphysiologic, such as the production of artificial pneumothorax or the restriction of the free influx of air into the lungs. On the other hand, the use of either of these methods for producing anoxia may give valuable information, for certain disease processes may simulate them. Many human beings have pneumothorax and, too, several conditions in the thorax may cause pronounced pressure on the trachea.

In the final analysis, while the use of the low-pressure chamber is presumably the most desirable method of producing experimental anoxic anoxia, there are occasions when the use of other methods to establish this condition are useful.

THE PRODUCTION OF ANEMIC ANOXIA

1. HEMORRHAGE

To produce acute anoxia it is necessary to withdraw relatively large quantities of blood from the body. If dogs are used as experimental animals, they may be bled either from the external jugular or by direct puncture of the femoral artery. In order to produce a chronic type of anoxia, it is necessary to withdraw blood from animals at periodic intervals. It has been observed that, if there is a reduction of about 20 per cent in the hemoglobin, there will be an increased pulse and respiratory rate.

2. BY CARBON MONOXIDE INHALATION

Since carbon monoxide produces an anemic type of anoxia, by combining with the hemoglobin, advantage may be taken of this to produce anoxia by allowing animals to breathe air or oxygen containing a given amount of carbon monoxide.

3. OTHER METHODS OF DESTROYING RED BLOOD CELLS OR DECREASING THE AMOUNT OF HEMOGLOBIN

Physical or chemical agents used to destroy red blood cells, such as the use of the x-ray or the use of phenylhydrazine, may produce side effects which may vitiate studies made principally on anoxia. Anemia produced by dietary control has the same objection.

In order to ascertain the degree of anoxia produced by anemia, it is necessary to determine the actual amount of oxygen in the blood.

THE PRODUCTION OF STAGNANT ANOXIA

Stagnant anoxia may be produced by impeding the flow of blood to an organ or a system of organs. The diameter of the vessel supplying the tissue under observation may be decreased either by partial ligation or by the use of a suitable clamp. If it is desired to produce a generalized anoxia, the aorta may be partly ligated or clamped or the aortic valve partly destroyed. It is difficult to produce experimentally the desired degree of anoxia; better quantitative methods need to be worked out for the production of this type of anoxia.

It should be mentioned that completely ligating a vessel, so that the tissues receive no blood at all, produces an unphysiologic condition; results obtained from such experiments should be interpreted with great care.

THE PRODUCTION OF HISTOTOXIC ANOXIA

The histotoxic type of anoxia is most satisfactorily produced by administering cyanides. In acute experiments cyanides may be given intravenously. In the author's experience, only about $1\frac{1}{2}$–2 mg. per kilo body weight can be given safely to a barbitalized dog. Narcotics, anesthetic agents, and certain other compounds may produce histotoxic anoxia, but nearly all these produce undesirable side effects; there are but few agents, if any, outside of the cyanides, which produce an unequivocal histotoxic anoxia.

GENERAL CONSIDERATIONS

FACTORS DETERMINING THE RESPONSE OF AN ORGANISM TO LOW OXYGEN TENSION

In discussing the effects of oxygen wants on physiologic processes it is generally recognized that four factors determine the response of an organism under low oxygen tension: (1) the suddenness of the production of oxygen want; (2) the degree of severity of oxygen want; (3) the duration of oxygen want; and (4) the physical condition of the body.

VARIABLES AT HIGH ALTITUDES

There are several variables at high altitudes which, in a measure, may influence physiologic processes. Schneider (31*) has listed these as follows: (1) lowered atmospheric pressure; (2) lowered partial pressure of oxygen; (3) temperature; (4) humidity; (5) increased intensity of sunshine; and (6) electrical conditions. It is known that the most important of these factors is the lowered partial pressure of oxygen. It is possible that some of the other factors may influence physiologic processes, but presumably they play subordinate roles.

ORGANIZED EXPEDITIONS TO HIGH ALTITUDES

During the past half-century a number of expeditions have been organized for the purpose of studying the physiology of high altitudes. It is worth while to call attention to the most important of these, since observations made by members of these expeditions are mentioned many times in this monograph.

Mosso in 1894 made studies on Monte Rosa (15,000 feet), and since then numerous other workers have made observations on this mountain; a rather extensive study was made by the Durchgeführten Monte Rosa Expedition in 1906. The findings of this expedition were reported by Durig in 1909, in *Physiologische Ergebnisse der im Jahre 1906*. Zuntz, Loewy, Muller, and Caspari led an expedition in 1901; their observations were published in 1906, in *Höhenklima und Bergwanderungen in ihrer Wirkung auf den Menschen* (Berlin: Bong, 1906).

* See p. 31 for bibliographical references.

In 1910 Zuntz and Barcroft and their associates made studies on the Peak of Teneriffe (12,000 feet). Douglas, Haldane, Henderson, and Schneider in 1911 made studies on Pike's Peak (14,100 feet). This was known as the Anglo-American Expedition. In the winter of 1921–22 Barcroft led an expedition to the Peruvian Andes; most of the observations were made at Cerro de Pasco (14,200 feet). This is sometimes spoken of as the Expedition of the Royal Society; there were, however, several Americans on this expedition. In 1931 Hartman led an expedition to the Himalayas which is known as the German Himalayan Expedition. In 1935 a group of ten men (led by Dill and Keys) made an expedition to the Chilean Andes; this was known as the International High Altitude Expedition to Chile.

The data obtained on these expeditions have enriched greatly the literature on oxygen want, and the scientific world is indebted to the individual members of these various expeditions for their painstaking observations, often made under the most adverse circumstances.

Besides the work of the members of the large organized expeditions to high altitudes, many individuals, working practically alone at high elevations, have made important contributions to our knowledge concerning anoxic anoxia. The various expeditions to Mount Everest, although not organized primarily to gather physiologic data, have contributed a great deal to our knowledge concerning the effect of extremely high altitudes on man. The observations, in this regard, made by Major Hingston, Colonel Norton, Dr. Somervell, and others are extremely valuable.

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EFFECT OF ANOXIA ON THE BLOOD

ERYTHROCYTES

Paul Bert in 1878, in his *La Pression barometrique* (12*), predicted with rare insight that the blood of animals, as well as of men, living at high altitudes would be found to have greater capacity for carrying oxygen than those living at lower levels. He believed this was brought about by the decrease in the partial pressure of oxygen at high altitudes and, further, that this phenomenon was an important feature in the acclimatization of animals in these regions. In order for this adaptation to take place, however, he thought residence at high altitudes would be required for several generations. In 1882 he (13) was able to prove his hypothesis by the discovery that the blood obtained from animals living at high altitudes in Bolivia actually had greater oxygen-carrying capacity than blood taken from animals at sea-level. The increased hemoglobin content of the blood of these animals gave them this ability.

A few years later, in 1890, Viault (85), during a three weeks' visit in Peru at an altitude of 14,400 feet, observed an increase in the number of red corpuscles per cubic millimeter in himself and in his companions. This work gave the final proof of the prediction first made by Bert 12 years before.

Considerable controversy arose over the work of Bert and Viault, but their findings have been corroborated repeatedly and are now generally accepted.

THE ORDER OF MAGNITUDE OF INCREASE IN ERYTHROCYTES PRODUCED BY ANOXIA

An enormous amount of data has been collected on the polycythemia produced by high altitudes since the original work of Bert in 1882. The data given in Table 4 are of interest since they give the findings obtained in well-known regions of the United States.

Table 5 shows the red blood cell count and the amount of hemoglobin at high altitudes in areas outside of the United States.

* See p. 55 for bibliographical references.

Table 4 indicates that there is a direct ratio between the number of red blood cells and altitude. Doubtless there is much individual variation, although Miss Fitzgerald (37) has formulated the law that

TABLE 4*

	Altitude (Feet)	Number of Red Blood Cells (Millions per Cu. Mm.)	Percentage of Hemoglobin (Av.)	Oxygen Capacity (Vols.)
Sea-level	0	4.5–5.4	100	17.0–18.7
Colorado Springs	6,000	5.5–6.3	110	20.0–21.7
Pike's Peak	14,100	6.0–8.2	144	27.4

*From *Air Service Medical* (Washington, D.C.: U.S. Government Printing Office, 1919), p. 143.

TABLE 5*

Locality	Investigator	Altitude		Red Blood Cell Count (Av.)	Hemoglobin (Av.)
		Feet	Meters		
1. Davos	Kuendig, Loewy, and co-workers	5,200	1,560	6,550,000	130 (Sahli)
2. Arosa	Eggers	6,000	1,800	7,000,000	
3. Mexico	Eggers	7,567	2,270	7,250,000	111 (Sahli)
4. Bolivian Andes	Viault	14,667	4,400	8,000,000	
5. Peruvian Andes	Barcroft	15,000	4,500	7,000,000	
6. Plateau of Pamir	Hingston	14,667	4,400	7,000,000	
7. Morococha (Peru)	Hurtado	16,667	5,000	6,660,000	15.93 gm.%
8. Plateau of Pamir	Hingston	18,500	5,500	Native Kirgises 7,920,000 Native Sarilol 7,600,000	

* Modified from A. Loewy and E. Wittkower, *The Pathology of High Altitude Climate* (London: Oxford University Press, 1937), p. 38.

for every 100-mm. fall in atmospheric pressure there is an average rise of 10 per cent hemoglobin. It has been pointed out by Loewy and Wittkower (65), however, that the increase in red blood cells at an elevation from 6,000 feet upward becomes comparatively unimportant. These authors feel that this diminution in the increase in cells beyond a certain limit is purposive, since, if the increase in cells became too great, the increased viscosity of the blood caused thereby

would make it difficult for the heart to maintain an efficient circulation. This has been denied by Dill (26), who points out that even a noticeable increase in red blood cells has but little effect on the resistance to flow of blood because of the axial flow in the arterioles and the ability of the capillary bed to adjust itself to the character of the blood passing through it. (Regarding blood viscosity, see p. 49.)

CHANGES IN SIZE OF RED BLOOD CELLS

It is stated by Loewy and Wittkower (65) that anisocytosis (inequality in the size of the cell) takes place at high altitudes. Hurtado (51) found a macrocytosis in the Peruvian natives. Some workers (31, 39) feel that the macrocytosis is due to stimulation of the red bone marrow by the anoxia. On the other hand, Smith and his associates (83) in 1924 reported that at an altitude of 11,000 feet the individual red blood cells were slightly smaller, although they were capable of holding the same amount of hemoglobin. It appears that further study is needed and that red cells should be measured in the same subject who had resided for some time at different altitudes.

INCREASE IN RETICULOCYTES

That there is a percentage increase in reticulocytes has been shown by a number of workers (4, 43, 54, 88). Normally there are about 50,000 reticulocytes in a cubic millimeter of blood; that is, they constitute about 1–1½ per cent of the erythrocytes. They are regarded as young red blood cells.

Barcroft (4) reported that in six Peruvian natives there was a reticulocytosis. There was, however, a noticeable individual variation; two natives showed only a moderate increase, but four showed an increase of over 175,000. In the natives there was an increased amount of red bone marrow, so that an excess of red corpuscles are discharged into the blood stream. It is generally thought, however, that the reticulocytes are not extruded in greater numbers than correspond to the increase in the number of red blood cells.

Experimentally, it has been shown that anoxia may produce a reticulocytosis. Gordon and Kleinberg (43) in 1937 kept guinea pigs for 5–14 days at a barometric pressure of about 375 mm. Hg (18,000 feet), and the reticulocyte count increased from 6 to 14 per cent.

THE QUESTION OF A DECREASED OXYGEN TENSION OR A LOW BAROMETRIC PRESSURE AS A CAUSE OF THE POLYCYTHEMIA

This question naturally arose after it was discovered that a polycythemia was produced by high altitudes. It is obvious that the problem could be solved by subjecting animals to low oxygen tensions while maintaining a normal barometric pressure. This can be done readily by diluting the atmospheric air with some inert gas such as nitrogen or by mixing oxygen and some inert gas in the desired proportions.

Sellier (82) in 1894 subjected birds and guinea pigs to a low oxygen tension but maintained a normal barometric pressure. He concluded that the polycythemia produced by high altitudes was caused by the low oxygen tension and that the barometric pressure was unimportant. His data, as he himself admitted, however, was inconclusive. In 1913 David (25) did similar work to that of Sellier and came to the same conclusion. Dallwig, Kolls, and Loevenhart (24) in 1915 felt that these data, too, were inconclusive; so they attacked the problem. They used rabbits, young dogs, and white rats. The animals were placed in a chamber so constructed that the oxygen tension could be reduced without changing the normal barometric pressure. It was found that when the animals were subjected to a normal barometric pressure, which contained a lowered oxygen tension, polycythemia was produced and, further, that the return to normal was slow (more than a month). They used this as striking evidence for the fact that the blood changes of high altitudes were due essentially to the low partial pressure of oxygen. Their well-controlled and exhaustive experiments, performed on several different species of animals, proved conclusively that polycythemia produced by high altitudes is due to oxygen want and not to a diminished barometric pressure.

THEORIES AS TO THE CAUSE OF POLYCYTHEMIA PRODUCED BY ANOXIA

Following the discovery that high altitudes were capable of producing polycythemia, a number of theories were advanced to explain the mechanism of the increased production. Among these were (1) an unequal distribution of erythrocytes throughout the body, (2) a

lengthening of life-span of the erythrocytes, (3) presence of an auxiliary or latent store of red blood cells, (4) irradiation by the more powerful sunlight rays at high altitudes, (5) an increased concentration of the blood, and (6) an acceleration of hematopoietic activity of the red bone marrow. Each of these theories will be considered briefly.

1. *An unequal distribution of red blood cells throughout the body.*—Experimental evidence was offered calculated to show that lowered partial oxygen pressure drove the red blood cells to the periphery at the expense of the more deeply situated vessels, so that the total red blood cell count would be unchanged. In 1901 Campbell and Hoagland (20) reported that animals which had been subjected to anoxia showed more erythrocytes in the vessels of the ear than in those of the mesentery. Foa (38) in 1904 reported that the ear veins of rabbits subjected to anoxia contained more erythrocytes than the blood from an artery. On the other hand, Dallwig, Kolls, and Loevenhart (24) in 1915, working with animals which had been subjected to anoxia, found that, within experimental limits, blood withdrawn from the marginal ear vein, carotid artery, and heart had the same count. These latter findings have been accepted, and it is no longer held that anoxia causes an unequal distribution of red blood cells throughout the body.

2. *A lengthening of life-span of erythrocytes.*—In 1895 Fick (36) suggested that the erythrocytes lived longer at high altitudes and and that this probably was the cause of the polycythemia found under these conditions. He offered no experimental evidence for this theory; and, up to this time, none has ever been produced. This theory, then, may be dismissed for lack of sufficient evidence.

3. *Presence of an auxiliary or latent store of red blood cells.*—It has been observed by a number of workers that in many instances anoxia produces practically an immediate rise in the hemoglobin and in the number of the red blood cells. This fact puzzled the early workers. Dallwig, Kolls, and Loevenhart (24) in 1915 definitely stated that their experiments threw no light on this phenomenon. Schneider and Havens (80), working on Pike's Peak in the same year, came to the conclusion that the increase in the amount of hemoglobin and in the number of red blood cells seen during the first two or three days was due to the body throwing into the circulation a

large mass of reserve red blood cells, to blood concentration, and to a stimulation of red bone marrow. They did not know, however, from where the increased red blood cells came. Various other investigators made unsuccessful efforts to find blood reservoirs in the body. In 1917 Scott (81) reported that nowhere in the body was he able to find masses of stored corpuscles. Three years later Lamson (61) also came to the conclusion that the body contained no reservoir of sufficient magnitude to influence appreciably the red cell count, and he stated that those conditions of acute polycythemia in which sufficient time had not elapsed for increased red blood cell formation were due to hemoconcentration. He believed the fluid loss occurred through the liver lymphatics. Smith and his co-workers (83) in 1924, working at an altitude of 11,000 feet and using the dye and carbon monoxide methods to determine blood changes, concluded that the rise in red blood cells and in hemoglobin were due to the production of more cells and not to redistribution.

Matters stood thus when Barcroft and his associates (11) in 1925 showed that, upon contraction, the spleen was capable of throwing into the circulation a large number of red blood cells. In the cat it was estimated that approximately one-sixth of the blood volume or one-third of the number of red blood cells can be expelled by the spleen. It was shown, furthermore, by Schafer and Moore (77) that anoxia causes the spleen to contract. The immediate rise in hemoglobin and number of red blood cells at high altitudes observed by various workers can be explained, then, by this action of the spleen. It is of interest to add, at this point, that the observations made by Schneider and Havens (80) that abdominal massage and muscular exertion are capable of augmenting the number of red blood cells can be explained on the basis of splenic contraction.

Whether there are any other organs in the body or other means by which the body can accumulate or store red blood cells remains a question. Krogh's (59) work on capillary circulation suggests that it is not impossible that in certain areas of the body considerable stores of red blood cells may lie in dormant capillaries. The capillaries in the skin may have such stores; and when the proper stimulus arises, these stored erythrocytes, lying in the dormant capillaries, could well augment the red blood cell count. No convincing proof, however, has been offered to show that this is true.

4. *Increased irradiation by the more powerful sunlight at high altitudes.*—In 1921 Kestner (56) suggested that it was not the decrease of oxygen pressure in the blood, as was generally supposed, which produced the polycythemia but rather the increased and more intense irradiation of the sun rays found at high altitudes. He postulated that the rays formed substances in the air which, when inhaled, stimulated the formation of red blood cells. It was suggested that these unknown substances were nitroxyl compounds. Further researches are needed, however, to ascertain how much importance should be ascribed to the role of the powerful sun rays found at high altitudes.

5. *An increased concentration of blood at high altitudes.*—Grawitz (44) in 1895 maintained that the polycythemia produced by anoxia was more apparent than real and attributed the increase in red blood cells and hemoglobin to a concentration of the blood. He postulated that the body lost more water at high altitudes than at lower levels.

Grawitz' theory was challenged by Loevenhart's group (24), who maintained that if his theory were correct the following would have to be true: (*a*) There should always be a parallel increase in the red blood cells and the hemoglobin. (*b*) Since the red blood cells and hemoglobin often increase 20 per cent, the blood would have to lose 20 per cent of its water; and, since this would have to come from the tissues, the whole body would have to lose this amount of weight. (*c*) If such a marked loss of water took place, there should be a noticeable increase in the specific gravity of the plasma and the material in solution. And lastly (*d*), the total determination of hemoglobin would show no increase. This group held that none of these propositions was in accord with the known facts.

Bunge (17) in the same year suggested that vasoconstriction took place at high altitudes and that the blood plasma left the vessels to go into the tissues. No acceptable evidence has been produced, however, that anoxia causes a long-continued vasoconstriction. Jacquet (52) in 1901 kept animals under a barometric pressure of 640 mm. Hg (5,000 feet) and found that not only the percentage of the hemoglobin but also the total mass of hemoglobin increased; the volume of blood, however, remained practically unaltered. Abderhalden (1) in 1902, working with animals at 6,100 feet, presented evidence to show that there would be a hemoconcentration at high

altitudes without overproduction. It was believed by Dreyer and Walker (32) that the change in blood volume was proportional to the area of the body surface. Douglas, Haldane, Henderson, and Schneider (30), after working on four men during a residence of 5 weeks on Pike's Peak, found that during the first days three of the subjects showed a diminished blood volume but that this was followed by an increase in the total amount of hemoglobin with a restoration of normal blood volume. Schneider and Havens (80) in 1915, also working on Pike's Peak, came to the conclusion that during the first few days there was a hemoconcentration.

Nature of mechanism of production of hemoconcentration.—The work of Dallwig, Kolls, and Loevenhart (24) and that of Gregg, Lutz, and Schneider (45) have shown that Grawitz' theory of hemoconcentration of the blood cannot be explained as a result of evaporation of water from the body at high altitudes. These workers kept both men and animals under such conditions that the perspiration and evaporation were normal or subnormal. The last-mentioned workers, without any noticeable activity of the sweat glands, obtained concentration within 15–20 minutes. They also showed that it could not be explained on the basis of increased activity of the kidneys, as suggested by observations made on aviators by Birley (14), since they found that hemoconcentration in aviators may also occur in 15–20 minutes, a time which is too short, and that the volume of urine eliminated was too small. Furthermore, a study of the weight of subjects before and after exposure to anoxia showed that the hemoconcentration was not due to a loss of water from the body. Neither can it be explained by changes in the blood pressure, since, under anoxic conditions, arterial pressure in many instances does not rise and may even fall.

Recent work by Lawless (63) in the author's laboratory has shown that if rats are subjected to anoxia there is a significant loss of water from the skin and from the muscles. This probably could account for slight losses of weight which have been observed in some animals following exposure to anoxia.

Smith, Belt, Arnold, and Carrier (83) in 1924, working at an altitude of about 11,000 feet, came to the conclusion that there was no blood-volume change within the first or second day at high altitudes.

Barcroft (5) has suggested that the possible methods of increasing the blood concentration at high altitudes may be divided into (*a*) emergency measures and (*b*) final measures. Under emergency measures he has listed: abstraction of water, opening of capillary areas, contraction of the spleen, and unrecognized methods; under final measures he has listed the activity of the bone marrow.

Today but little can be added to what was known nearly 20 years ago. Barcroft (5) has well stated the fact that "in the discussion of how the increase is brought about, one must recognize at once that there is probably no one method. The body works as a team and several quite different mechanisms may be brought into play, each of which, because it is asked to contribute a little, suffers no great dislocation of function."

In summary, it may be said that if it is accepted as proved that a certain amount of hemoconcentration may take place at high altitudes, it still cannot account for the pronounced rise in the number of red blood cells which so often takes place. Hemoconcentration may be a factor, but it certainly is not a major one.

6. *An acceleration of hematopoietic activity of red bone marrow.*—The early workers—Bert (12) in 1878, Viault (85) in 1892, and Miescher (63) in 1893—all held that the increase of erythrocytes at high altitude was due to the low oxygen tension stimulating the red bone marrow.

Miescher felt that the red bone marrow normally existed under a relative oxygen want and that this maintained the bone marrow in a condition of activity, so that the erythrocytes and hemoglobin were being produced constantly. When the body suffered from anoxia, however, the bone marrow was stimulated to increased activity.

Zuntz *et al.* (89) in 1906 reported histological studies on the bone marrow of dogs at sea-level and in animals acclimated to high altitudes. In the latter a decrease in fat cells and an increase in the blood-forming elements were found.

Nasmith and Graham (71) in 1906 and Nasmith and Harrison (72) in 1910 studied the effect of chronic carbon monoxide poisoning on guinea pigs and rabbits and found noticeable increases in the red

blood cells and hemoglobin. They likened the effect of carbon monoxide poisoning to that produced by high altitudes.

Burker, Ederle, and Kircher (19) in 1913 lessened the respiratory surface of the lungs by producing a unilateral pneumothorax in dogs and rabbits; observations were also made on man. They reported marked increases in the red blood cells and the hemoglobin. Their method has been criticized, however, since a collapse of one lung introduces marked abnormalities.

In 1913 Laquer (62) reported that dogs which had been deprived of hemoglobin by pronounced hemorrhage took 27 days at sea-level to regenerate their hemoglobin, but on Monte Rosa (15,000 feet) only 16 days were required. In the same year Schneider (79), by determining the changes after descent in a man who had resided at an altitude of 14,000 feet, proved there had been an overproduction of erythrocytes and hemoglobin. The total capacity of the blood decreased about 12 per cent in the course of 10 weeks.

In 1915 Dallwig, Kolls, and Loevenhart (24), working with animals which had been subjected to low oxygen tensions, found a large increase in hemoglobin per kilo of body weight and a noticeable extension of the red bone marrow. These workers maintained that the low partial pressure of oxygen stimulated the red bone marrow and that their views were closely in accord with those of Miescher (68).

It was shown by Haldane and Priestley (47) in 1905 that before the respiratory center is stimulated by oxygen want the respired air must fall to 13 per cent of an atmosphere. Dallwig *et al.* (24) found that the bone marrow was stimulated at 14 per cent oxygen. It was concluded that, while the bone marrow might be slightly less sensitive to oxygen than the respiratory center, practically there was but little difference.

In order to show that bone marrow was not depressed by severe anoxia, the last-mentioned workers kept animals at 6 per cent oxygen for a week; even at this severe degree of anoxia the bone marrow was still stimulated. These workers also studied the effect of carbon dioxide on the bone marrow. Animals were allowed to breathe air which contained from 0.5 per cent to 1 per cent carbon dioxide. This concentration of carbon dioxide slightly stimulated the bone marrow,

but they concluded that it was far less sensitive to carbon dioxide than was the respiratory center.

Further proof that the activity of the red bone marrow is stimulated by lowered partial pressure of oxygen is the finding of numerous reticulated cells in the circulation at high altitudes. It is known that reticulated cells are young red corpuscles; normally a cubic millimeter of blood contains about 50,000 of such cells. A noticeable increase in reticulated cells was found in some of the members of the Peruvian Expedition of 1921–22. In two members of the party over 175,000 reticulated cells per cubic millimeter of blood were found. The interpretation is that the red bone marrow is stimulated by the anoxia and that these cells are thrown into the general circulation before they have time to mature.

In general, it may be said, then, that there is overwhelming evidence that at least one cause, and presumably the major one, for the polycythemia of high altitudes is the overactivity of the red bone marrow. However, the exact nature of the stimulus of the red bone marrow has not been determined.

TIME NEEDED FOR THE DEVELOPMENT OF INCREASE IN ERYTHROCYTES UNDER ANOXIC CONDITIONS

While there has been some divergence of opinion by various workers (1, 30, 34, 73, 80, 83) regarding the exact time necessary for the development of polycythemia at high altitudes, it is generally agreed that it may develop fairly rapidly. It is influenced by the rate and height of ascent, by the physical condition of the subject, and, in a measure, by the amount of physical effort made.

Experimentally, if oxygen want is induced rapidly, there may be a rapid increase in red blood cells and hemoglobin, as was shown by Gregg, Lutz, and Schneider (45) in 1919 with the use of the low-pressure chamber. When individuals were subjected to pressures corresponding from 15,000 to 18,000 feet at a rate of ascent of 1,000 feet per minute, the erythrocytes and hemoglobin rose within a period of 30–60 minutes in 78 per cent of the men examined. It is likely that this increase was due to the contraction of the spleen.

Richards (75) (see Fig. 7) found that his hemoglobin increased in 5 days from an average of 101 to 129 per cent.

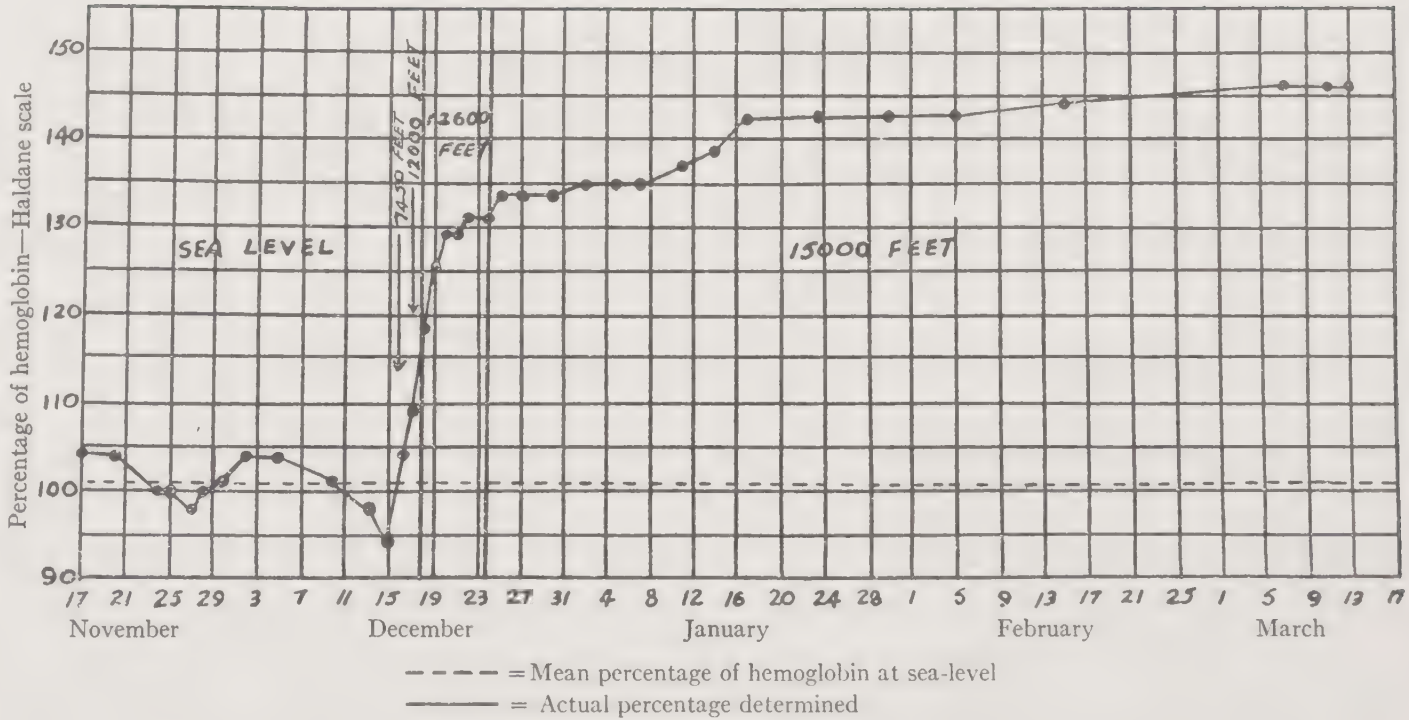

FIG. 7.—Showing effect of altitude on hemoglobin. (From Barcroft, *The Respiratory Function of the Blood* [Cambridge University Press, 1925], Part I, "Lessons from High Altitudes," p. 139.) (Originally published by the Royal Society: Richards, *Philosophical Transactions*, B, 203, Appen. 1, pp. 203, 316.)

Experimental work done on animals (24) subjected to anoxia has, for the main part, corroborated the findings in man; that is, an increase in both red blood cells and hemoglobin were manifested within a relatively short time.

Reports have been made (70) of individuals whose hemopoietic system did not respond well to increased altitudes. The interpretation was that the tardiness in blood changes was due to the relatively poor physical condition of the subjects. Reports have been made by Hurtado and by Dill (p. 147) which indicate that not all apparently normal individuals show a polycythemia at high altitudes. There are also reports in the literature which indicate that strenuous exercise at high altitudes may cause a fall in the hemoglobin content of the blood. Cohnheim and Kreglinger (22) reported that a hard climb in the Alps to an approximate altitude of 10,000 feet produced a distinct fall in the hemoglobin. A similar experience was reported by Gross and Kestner (46). These apparent paradoxical findings can best be explained on the basis that the extremely severe exercise destroyed the red blood cells faster than the red bone marrow could produce them even under the stimulatory effect of high altitudes. The explanation given by these authors, however, is not complete, since they did not take into account that under anoxic conditions the spleen contracts.

In summary, it may be said that it is generally considered that the usual response of a subject during residence at high altitudes is that during the first 2–4 days there is a rapid increase in the number of red blood cells and in the percentage of hemoglobin, after which the increase is more gradual; equilibrium, however, is not established for several weeks or even months.

POSTEXPERIMENTAL BLOOD CHANGES

In working with animals Loevenhart's group (24) found that during the first and second days after removal from the low-pressure chamber a further increase in the red cell count frequently was observed. Investigators working with man on the polycythemia produced by high altitudes have also observed this. It appears, then, that the stimulus the red bone marrow received by the anoxia persists a little while even though the subject returns to sea-level.

TIME NEEDED TO RETURN TO NORMAL VALUES

Experimentally, it was shown by Loevenhart's group that after the animals were removed from the low-pressure chamber it often required more than a month for the erythrocytes to reach the level obtained before the exposure to an atmosphere of low oxygen tension. Similar results have been observed by workers who were studying the polycythemia in man at high altitudes.

HEMOGLOBIN

Ever since Paul Bert published his *La Pression barometrique* in 1878, it has been known that anoxia not only produces an increase in the number of red blood cells but also an increase in the amount of hemoglobin. Since Bert's work many investigations have been made on this problem. It has been shown conclusively that during anoxia there is an increase in the total amount of hemoglobin per kilo of body weight.

Dallwig *et al.* (24) in 1915, in experiments on rats, found that if they were kept for 3 weeks at 10 per cent oxygen at atmospheric pressure, they had 43 per cent more hemoglobin per kilo of body weight than animals kept at ordinary atmospheric conditions. Their findings corroborated the early reports of Jacquet and Suter (53) made in 1898 and that of Abderhalden (1) in 1902. The members of the Anglo-American Pike's Peak Expedition (30) definitely showed that in man not only the proportion of red blood cells but also the total quantity of hemoglobin in the circulation increased.

Miss Fitzgerald (37) has formulated a law that among acclimated inhabitants there is an average rise of about 10 per cent in hemoglobin for every 100 mm. Hg fall in barometric pressure. This rule applies to both sexes.

A classical example of the rise in hemoglobin produced by high altitudes is that of Mr. J. Richards, a mining engineer, who, at the request of Dr. Haldane, made observations on his own blood at varying altitudes up to 15,000 feet in the Bolivian Andes. Figure 7 shows that the hemoglobin continued to rise until it apparently reached its maximum (146 per cent) after a sojourn at 15,000 feet for about 80 days. The reader is also referred to Table 4, which shows the amount of hemoglobin at elevations of 6,000 and 14,100 feet.

The increase of hemoglobin at high altitudes presumably cannot be explained by a shrinkage of the plasma volume any more than can the increase in the number of red blood cells (see p. 39). Haldane and Priestley (48) have stated, however, that when a rapid increase of the hemoglobin occurs it is brought about mainly by the disappearance of the plasma, owing to a pressor reaction of the vasomotor center; they believed an increased filling of the capillaries occurs and that a loss of liquid of the blood follows.

EFFECT OF AIRCRAFT ASCENT ON THE NUMBER OF RED BLOOD CELLS AND THE AMOUNT OF HEMOGLOBIN

A number of years ago several workers (23, 41, 42) reported increases in the red blood cells and hemoglobin during balloon and airplane flights. Some of this early work was criticized since the determinations were made in open cockpits, and it was felt that the wind caused such rapid evaporation of the freshly drawn blood that the count was in error. As a matter of fact, recent workers (Fitzgerald, Schneider, McFarland, and others) likewise have reported increases in red cell count and in hemoglobin during airplane flights.

Armstrong and Heim (3) have found, however, that exposure for a 4-hour period to a simulated altitude of 12,000 feet for three consecutive days showed a decrease, rather than an increase, in the amount of hemoglobin and in the red cell count. These observers feel that if the work of previous investigators who have reported an increase in the red blood cell count and in the amount of hemoglobin be critically examined it will be found that their work was not carefully controlled or that they reported an atypical individual response or took their observation after an abnormally prolonged exposure to an individual flight. Undoubtedly, one reason for the discordant results reported is that various investigators were working with different altitudes. Obviously, more work is needed on this problem.

RELATION BETWEEN INCREASE IN NUMBER OF ERYTHROCYTES AND THE AMOUNT OF HEMOGLOBIN

It has been contended by some authors (18, 40, 72, 73, 78, 86) that the increase in red blood cells stimulated by anoxia exceeded that of the hemoglobin, while others (24, 33) found the opposite true, namely, a smaller increase in the number of erythrocytes than in the

amount of hemoglobin. On the other hand, reports made by the members of the Anglo-American Pike's Peak Expedition (30), as well as those of other workers (1, 18, 21, 83), tend to show that the red blood cells increase in equal proportion with the hemoglobin. Recent work favors this view.

COLOR-INDEX OF BLOOD AT HIGH ALTITUDES

Since it is now generally accepted that the red blood cells increase in equal proportion to the hemoglobin, there is no change in the color-index. It has been reported, however, that what is termed the *color-volume ratio* does increase at high altitudes (71).

EFFECT OF ANOXIA ON THE BLOOD PLATELETS

The effect of anoxia on blood platelets has engaged the attention of relatively few workers. It has been found that anoxia causes the number of platelets to increase. A tremendous augmentation at an altitude of 14,000 feet was reported by Kemp (55) in 1903. In 1914 Webb, Gilbert, and Havens (87) counted the blood platelets on one hundred college students residing at sea-level and obtained an average count of 302,000 per cubic millimeter. The platelet count for one hundred men at an altitude of 6,000 feet was found to be 340,000 per cubic millimeter. The reason for the increase is not known, but it has been postulated that anoxia is capable of stimulating the production of megacaryocytes.

EFFECT OF ANOXIA ON THE WHITE BLOOD CELLS

In general, it may be said that reduced atmospheric pressure has no important effect on the number of white blood cells. The differential count, however, may show some variation. There is considerable evidence that there is a relative increase in the number of large lymphocytes at the expense of the polymorphonuclear cells, so that the total count does not materially change.

Hurtado (51) in 1932 determined the leukocyte count in one hundred and twenty normal Peruvian natives who lived at an altitude of 14,890 feet (410 mm. Hg barometric pressure). The white blood count varied within normal limits, but there was a slight tendency for it to be low. He did not find an increase in the lymphocytes. In fifteen cases 28 per cent of the polymorphonuclear neutrophils were

found to be immature, although no nucleated red blood cells were observed. The histiocytes found in the peripheral blood were increased. He suggested that, since these cells probably were derived from the reticulo-endothelial system, their increase indicated a sign of overactivity of this system.

The most recent experiments on animals are those of Meyer, Severs, and Beatty (67), made in 1935. Rats and guinea pigs were subjected to a reduced atmospheric pressure. The rats were subjected to atmospheric pressures of 422, 352, and 282 mm. Hg corresponding approximately to altitudes of 15,000, 20,000, and 25,000 feet, and were kept at this level for a week. The guinea pigs were kept for only 42 hours at a level of 422 mm. Hg. It was concluded that the temporary leukocytosis following reduction in air pressure was due to the emptying of reservoirs of cells, such as those of the spleen, liver, and lungs; and the subsequent leukopenia, as resulting from a functional depression of the bone marrow and lymph nodes. These authors stated that the discordant results reported by previous workers doubtless could be explained on the basis that it was not recognized that anoxia first produced a lymphocytosis, followed by a leukopenia. No consistent changes in the differential blood count in their experimental animals could be found.

BLOOD VISCOSITY AT HIGH ALTITUDES

Since there is an increase in the number of red blood cells at high altitudes, it would be expected that the viscosity of the blood would be increased. That this is true has been shown by Hurtado (51), who determined the viscosity of the blood in one hundred and thirteen native Peruvian Indians. A Hess viscosimeter was employed, and distilled water was used for comparison. The mean value was found to be 8.6; and the variations, from 5.2 to 15.2. This is a distinct increase, since the viscosity at sea-level is about 5.1, with variations from 4.7 to 5.9.

The serum viscosity was found to be within normal limits. Hurtado points out that normally the viscosity of plasma exceeds that of serum by 0.2–0.3, but at high altitudes this relationship is reversed. He also found a relationship between the red blood cell count and blood viscosity but none between serum and plasma viscosity and level of red blood cell count.

It is of interest to pursue the question of blood viscosity at high altitudes somewhat further. It has been shown by Brundage (16) that an increase of one-third in the proportion of red blood cells increased the viscosity of the blood about three times. As pointed out clearly by Dill (27), if the resistance to flow within the body is relatively proportional to the increase of red blood cells, the work of the heart at high altitudes would be out of proportion to any advantage gained by the increased number of erythrocytes.

It has been found, however, that the law of Poiseuille is not applicable to a nonhomogenous fluid such as blood. When the blood flows through the small arterioles, where the greatest drop in pressure occurs, Fahraeus and Lindquist (35) found that, as the diameter of a capillary tube approaches 0.03 mm., the measured viscosity approaches that of plasma. Fahraeus believes that the plasma moves slowly along the periphery in the arterioles, but there is an axial flow of red blood cells. Now, when the blood enters the capillary bed, although the resistance to flow in a given capillary must be approximately proportional to the number of red cells, some of the capillaries which have been lying dormant may open up so that a large factor of safety is provided. That there are dormant capillaries has been shown by the pioneer work of Krogh (59). It is thought, then, that the increase in the number of red blood cells produced by anoxia does not throw an extraordinary burden on the circulatory system. There is still some divergence of opinion about this, however, and the matter cannot be regarded as entirely settled.

ANOXIA AND SPECIFIC GRAVITY OF THE BLOOD

As would be expected, the specific gravity of the blood is increased at high altitudes. This is doubtless due to the increase of the number of red blood cells and blood platelets. The normal specific gravity of the blood may be given as 1.055; at Colorado Springs (6,000 feet altitude) it was found to be 1.067; and at Pike's Peak (14,100 feet altitude), 1.073 (2).

FRAGILITY OF RED BLOOD CELLS AND ANOXIA

Hurtado (51) determined the fragility of red blood cells in fourteen normal native Peruvian Indians. An increased resistance of

red blood cells to hypotonic sodium chloride solution was found. He felt this was due to the young blood cells (not reticulated cells). It is of interest in this connection to point out that Minot and Buckman (69) obtained similar results in polycythemia vera.

COAGULATION TIME OF THE BLOOD AND ANOXIA

Since anoxia increases the number of blood platelets, it is not illogical to assume that the coagulation time would be decreased. Hurtado (51) determined the coagulation time of the blood in ninety-five normal Peruvian Indians and found a tendency for a rather short coagulation time at high altitudes. He suggested that it was due to an increased blood viscosity, but no correlation between coagulation and the level of the red cell count has been found.

OXYGEN CONTENT AND OXYGEN CAPACITY OF BLOOD AT HIGH ALTITUDES

It is necessary to distinguish clearly between *oxygen content* and *oxygen capacity*. By the former is meant the actual amount of oxygen found present in the blood under the specified condition, whereas by *oxygen capacity* is meant the amount of oxygen the blood can actually contain if it is exposed to air. The percentage saturation is computed as follows: (Oxygen content/Oxygen capacity) × 100. Normally, the following relationship exists: (19/20) × 100 = 95 per cent saturation; that is, under normal conditions the arterial blood is 95 per cent saturated with oxygen.

It is believed that the increase in hemoglobin and erythrocytes at high altitudes enables the blood to have an increased concentration of oxygen with a subsequent increased oxygen supply to the tissues. The oxygen content of the blood at high altitudes has been investigated by several workers.

Hurtado (51) found in the Peruvian natives an oxygen content from 16.5 to 17.5 volumes per cent with an oxygen capacity of 19.2–20.0 volumes per cent, which corresponds to an average saturation of 86 per cent in arterial blood. Barcroft, also working with Peruvian natives, obtained virtually the same results. Hurtado's figures show that the oxygen capacity and the degree of saturation (91 per cent) of the arterial blood in lowlanders who ascend to high altitudes are

higher than in natives living in such districts. Stammers (84) at Johannesburg (5,700 feet altitude) found the saturation in arterial blood within limits of normal lowland values.

It would seem that higher values should be found in the natives than were reported by Hurtado and by Barcroft. Their findings indicate that there are other factors of adaptation to high altitudes than the oxygen content of the blood. In Keys's (57) group the oxygen content of the blood increased an average of 25 per cent. As Keys suggests, this increased oxygen capacity of the blood overcomes, in part, the handicap of low arterial oxygen saturation; other factors, however, are also at work, and one he suggests is that tissues during acclimatization may become habituated to live on oxygen supplied at a lower pressure.

In general, it may be said that the oxygen capacity of the blood increases with the number of red blood cells. For example, it was found that at sea-level it was 17.0–18.7, at Colorado Springs (6,000 feet) 20.0–21.7, and at Pike's Peak (14,100 feet) 27.4 (see Table 4). Dill (28), too, has strongly emphasized that the increase in red cell count is an excellent measure of increase in oxygen-combining capacity.

It must be emphasized, however, that while it is believed that the amount of oxygen present in the blood is important it is still more important that the oxygen be supplied at a definite pressure. It is for this reason that we must look for other factors; and the one which was first suggested by Paul Bert, that in the process of acclimatization the tissues may become habituated to live on oxygen supplied at a relatively low pressure, may be a very important one.

THE EFFECT OF ANOXIA ON THE OXYGEN DISSOCIATION CURVE AFFINITY OF HEMOGLOBIN FOR OXYGEN AT HIGH ALTITUDES

Since the blood at high altitudes becomes abnormally alkaline, owing to the increased pulmonary ventilation, it would be expected that the oxygen dissociation curve would shift to the left and that the affinity of the hemoglobin for oxygen would be increased. The observations made by Barcroft and his co-workers on the Peak of Teneriffe, at altitudes of 7,000 and 11,000 feet, and later on Monte

Rosa (9) indicated that at high altitudes there was no increase in the affinity of the hemoglobin for oxygen. Furthermore, in 1911 Douglas, Haldane, Henderson, and Schneider (30), members of the Anglo-American Pike's Peak Expedition (altitude 14,100 feet), found no appreciable change in the position of the oxygen dissociation curve of the blood equilibrated with alveolar air.

In 1922, however, the members of the Peruvian-Andean Expedition (6), led by Barcroft, obtained results indicating that there was a shift of the oxygen dissociation curve to the left after the individuals had lived for some weeks at an altitude of 14,200 feet. The interpretation that Barcroft and his colleagues made was that at high altitudes there was a distinct increase in the affinity of hemoglobin for oxygen. These findings led to a long, friendly argument between J. S. Haldane and Barcroft as to whether or not the blood of acclimatized man in high altitudes seizes oxygen more avidly.

The problem was studied further by Dill *et al.* (29) in 1929 in the Colorado Rocky Mountains. These workers could find no change in the affinity of hemoglobin for oxygen at an elevation either of 10,000 or of 14,000 feet. In 1933, however, Buikov and Martinson (15), working at moderate altitudes (2,000–7,000 feet), published results supporting the findings of the members of the Peruvian-Andean Expedition. Keys *et al.* (58), however, have criticized the adequacy of the data of these last-named workers.

The question was reopened by Barcroft and his co-workers (7, 10, 66), who attacked the problem from a different angle. It was found that in the goat the fetal blood had a greater affinity for oxygen than did the maternal blood. Hall (49) reported a similar relation between the blood of the embryonic chick and that of the mature hen. These findings doubtless stimulated Barcroft to give the title of one of his addresses as "Everest in Utero."

Further interesting observations concerning the affinity of fetal hemoglobin for oxygen were made by Roos and Romijn (76) in 1938. They reported that in the whole blood of calves there was a pronounced avidity for oxygen at low tensions. The oxygen dissociation curve of the fetus was found to be well to the left of the curve of its mother. These authors maintained that this was inexplainable on the basis of greater alkalinity of the mother's blood but that it was

due to a difference between the properties of fetal and maternal blood.

In point of fact, Barcroft (8) in 1934 wrote in his *Features in the Architecture of Physiological Function:* "Indeed the conception of there being more than one sort of hemoglobin even in ordinary blood is not revolutionary; it may be that the difference between foetal and maternal hemoglobins lies in the proportion in which the two are mixed." And Krogh (60) in 1941, in his *Comparative Physiology of Laboratory Mechanisms*, wrote: "The foetal blood shows a definitely steeper dissociation curve than the blood of the mother, which has turned out to be the presence of a different hemoglobin."

It may be accepted, then, that the fetal blood, at least in some animals, shows a greater affinity for oxygen than the maternal blood.

Valuable studies made on the position of the oxygen dissociation curve at extremely high altitudes were reported in 1936 by members of the International High Altitude Expedition to Chile (58, 50). Data were obtained from whole arterial blood on ten men who had been at various levels of altitude up to 19,816 feet over a period from 2 to $3\frac{1}{2}$ months. No tendency was found toward an increased affinity of hemoglobin for oxygen, but rather a uniform tendency in the opposite direction. Up to an altitude of about 14,000 feet the oxygen dissociation curves were displaced to the left of sea-level points, but above that altitude the curves were placed increasingly to the right of these points.

These investigators also determined the position of the oxygen dissociation curves for eleven long-time residents at altitudes up to 17,520 feet. The majority of these men had performed hard labor at an altitude of 18,700 feet. No appreciable changes were observed in the position of the oxygen dissociation curves of these men. These data are interesting, indeed, and point strongly to the fact that even at extremely high altitudes the affinity of hemoglobin for oxygen apparently remains unchanged.

Keys, Hall, and Barron (58) point out that the results which they obtained are not entirely inconsistent with those of Douglas, Haldane, Henderson, and Schneider and those of Barcroft and his coworkers. Neither of these two latter groups of investigators studied the position of the oxygen dissociation curves beyond 14,200 feet.

It was only above this altitude that Keys and his colleagues found a slight shift of the curves to the right.

In summary, then, there is considerable evidence that at altitudes up to 14,000 feet there may be a slight shift of the oxygen dissociation curve to the left; but beyond this altitude, according to the work of Keys, Hall, and Barron, there is a tendency for the curve to shift to the right. It appears from these findings that there is no change in the affinity of hemoglobin for oxygen at extremely high altitudes. In view of the importance of this problem and because of the inconstant results reported at moderate altitudes and the paucity of data at extremely high altitudes, it would be distinctly worth while to secure more data on the position of oxygen dissociation curves at various altitudes, especially those over 14,000 feet.

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CHEMICAL CHANGES IN THE BLOOD DURING ANOXIA

A considerable amount of work has been reported on the acid-base balance of the blood during anoxic anoxia, but relatively little has been reported on other chemical changes which take place during this condition.

Acid-base balance of the blood.—It is important to discuss in some detail the effect of anoxia on the acid-base balance of the blood. This problem is related intimately to the chemical changes brought about in the blood by the hyperpnea produced by anoxic anoxia; so some reiteration will be necessary when the effect of anoxia on the chemistry of respiration is discussed (p. 118).

The early view was that anoxic anoxia was associated with acidosis, which gave rise to the so-called "acidosis theory." In 1910 Ryffel (58*), however, could find no excess of lactic acid, or of any other abnormal acids, in the urine or the blood in subjects who had been exposed either to a low-pressure oxygen tension in a respiration chamber or to high altitudes. It appeared, then, that the "acidosis theory" could not be explained on the basis of accumulation of abnormal acids in the blood.

On the other hand, in 1915 Hasselbalch and Lindhard (32), working with a steel chamber, found that low oxygen pressures produced a diminution in the excretion of ammonia. They felt that the acidosis of high altitudes was due to diminished formation of ammonia by the body.

In 1919 Haldane, Kellas, and Kennaway (30) found that, even if oxygen pressure was lowered but slightly, there occurred a marked diminution in the excretion of acid and ammonia and that the urine became alkaline in reaction. This made the "acidosis theory" no longer tenable, and so it gave way to the "alkalosis theory." These illuminating experiments threw a great deal of light on the chemical changes which take place in the body during anoxia and helped ex-

* See p. 70 for bibliographical references.

plain certain alterations in breathing during anoxic anoxia, as well as the changes which take place during acclimatization.

Henderson (34, 35) and later Haggard and Henderson (29) independently reached the same conclusion as did Haldane and his coworkers, namely, that there is an alkalosis and not an acidosis at high altitudes (in spite of a reduced alkaline reserve in the blood). These and other studies led to the modern conception of the chemical changes which take place in the blood during anoxic anoxia.

The changes which interest us here, however, are only those which influence the acid-base balance of the body. It is known that the hyperventilation produced by anoxia produces a lowering of the alveolar carbon dioxide tension and, consequently, a lowering of the carbon dioxide arterial tension. By this means an alkalosis is produced. The kidneys, in an effort to maintain an acid-base balance, secrete more base. Sundstroem (63), in 1919, was one of the first workers to make a relatively complete study of the excretion of acids and alkaline elements at high altitudes. He reported some increases in the excretion of sodium and potassium.

It is thought that the excretion of bicarbonate by the kidney continues until the plasma bicarbonate is reduced by nearly the same proportion as the carbon dioxide tension; and, as a consequence, it is deemed that there is only a slight increase in the pH of the blood. Whether or not there actually is an appreciable change of hydrogen-ion concentration in the body in rest during anoxic anoxia has been of great interest to a number of physiologists.

Barcroft and the members of his expedition to the Peruvian Andes in 1921–22 were greatly interested in this problem, and in his monograph Barcroft (5) states that it was for the purpose of finding this out, more than any other, that they desired a well-equipped laboratory for their expedition. The results they obtained were not clear cut, but their data indicated slight increases of pH (0.00–0.15). Barcroft felt that they had offered no evidence that the blood was more acid at high altitudes than at low ones when the body was at rest. During exercise, however, they found well-marked differences; at high altitudes the changes in the hydrogen-ion concentration were produced by a less amount of work than at lower levels.

Koehler, Brunquist, and Loevenhart (47) allowed young pigs to

breathe air containing 5–8 per cent oxygen (38–40 mm. oxygen tension) and obtained a pH increase of 0.11–0.13. In 1932 Henderson and Radloff (38) reported work on the acid-base balance of the blood during progressive decrease of oxygen. They found that while the oxygen was above 8 per cent there was an alkalosis but that if the oxygen fell below 8 per cent an acidosis was produced.

Recent observations by Keys *et al.* (45) have shown that the blood becomes more alkaline up to an altitude of 12,000 feet (483 mm. Hg barometric pressure); above this altitude there is either no further change or a return to normal.

From the available evidence it may be said, then, that until very severe degrees of anoxia are produced there is an alkalosis of the blood, which is only partly compensated for by a fall in plasma bicarbonate.

It is known that in extreme anoxia the alkalosis is replaced by an acidosis which becomes more marked as death approaches. The low oxygen pressure probably interferes with the proper combustion of the carbohydrates in the tissues, and the lactic acid formed produces an intense acidosis. As death approaches, the respiratory center fails, so that the carbon dioxide is no longer given off by the lungs; and this, added to the increased carbon dioxide accumulation in the tissues, causes an extreme reduction in the pH of the blood. Loevenhart and his co-workers (47) found that anoxic anoxia can produce more marked acidosis in the body than any other condition. In their experiments with pigs they obtained a pH as low as 6.7, and the carbon dioxide combining power was depressed to 9.8 volumes per cent.

It should be mentioned here, however, that Loevenhart and his associates (47) always felt that, in spite of the soundness of the "alkalosis theory," anoxic anoxia was fundamentally an acidotic process and that, as soon as oxygen want appeared, acid production in the cell began. The effect was masked, however, by the loss of carbon dioxide in the initial hyperventilation period.

In the experiments reported by Loevenhart's group no determination was made as to whether the acidosis was due to alkali loss or to the increased production of acid metabolites. They could not, however, find sufficient lactic acid in the blood to account for the severe acidosis. On the other hand, Macleod (49), working on anoxia and

shock, reported distinct increases in lactic acid production in the blood. The validity of his results, however, have been challenged.

It is obvious that more work is needed to determine the actual cause of the intense acidosis seen in the terminal stages of acute anoxic anoxia. There is considerable evidence by a number of reliable investigators that the acidosis cannot be accounted for by the accumulation of lactic acid. It seems that other acids must be sought; it would be well to investigate the amounts of aceto-acetic acid and beta-hydroxybutric acid; and in the light of recent work on the chemistry of muscle contraction the presence of phosphoric, adenylic, glycerophosphoric, and pyruvic acids and perhaps others should be investigated.

Alkaline reserve during anoxia.—It was shown as early as 1904 by Galleotti (25) that the titration alkalinity of the blood was diminished by exposure to low pressures in a steel chamber or at high altitudes.

According to Peters and Van Slyke (57), there is but little change in the alkaline reserve during the first hour or so of anoxic anoxia—merely a decrease in carbon dioxide tension, owing to the accelerated respiration, and a consequent increase in pH. After a few hours the alkaline reserve begins to fall—the extent, of course, depending upon the severity of the anoxia. It already has been mentioned that Loevenhart's group (47) found that in the terminal stage of anoxic anoxia the carbon dioxide combining power was depressed to 9.8 volumes.

Most observers have found a decreased alkali reserve in conditions of carbon monoxide poisoning; the interpretations of their results, however, have varied (29, 44, 53, 64).

The formation of lactic acid during anoxia.—Although the effect of anoxia on lactic acid production in the body has been considered briefly in the discussion of the acid-base balance of the blood, it is of interest to consider this in somewhat more detail.

Since it is known that lactic acid develops in the blood during exercise, it is not illogical to suppose that its production might increase during oxygen want. As a matter of fact, as early as 1891 Araki (2) reported that in acute oxygen want large quantities of lactic acid were produced in the body. In 1908 Boycott and Haldane (12) be-

lieved that the hyperpnea, seen during anoxic anoxia, was produced by the increased production of lactic acid sensitizing the respiratory center to carbon dioxide.

That at moderately high altitudes (10,000 feet) lactic acid does not accumulate in the blood was shown by Barcroft *et al.* (7) in their expedition to Monte Rosa. At 15,000 feet altitude Barcroft observed a suggested increase of lactic acid production, although there was no certain indication of this. As a point of fact, it was rather generally accepted that oxygen want produced an increase in lactic acid during anoxia; and this, in part, gave rise to the "acidosis theory," previously discussed. Macleod (49) in 1921 believed that there was an excess of lactic acid during anoxia and that this aided in neutralizing the relatively increased base. Sundstroem (63) claimed, however, that there was no increase of lactic acid production at high altitudes.

Experimentally (43), it has been shown in the turtle that complete anoxia for several hours may cause an increase of the lactic acid in the blood to almost 1,000 mg. per cent. The turtle is an animal which can withstand complete anoxia for about 30 hours, and so it is quite unlike a mammal. The results obtained by working with it in this instance are not of practical interest. They do show, however, that during severe anoxia there may be a great rise in blood lactates.

In 1934 Henderson and Greenburg (37) reported that it was only when the oxygen in the inspired air became less than 7 per cent that an increase in lactic acid in the blood developed.

Henderson (36) has written: "There is no increase of lactic acid in the stages of asphyxia in which respiration is increased. Lactic acid appears in the blood in large amounts only in the final stage in asphyxia, in which respiration is depressed."

The important observations made by Edwards and his co-workers (10, 20, 21) have added to our knowledge concerning the production of lactic acid at high altitudes. They found that after severe exercise at an altitude of 12,000 feet the blood lactate was lower than after severe exercise at sea-level; that following exercise at 15,000 feet it was still lower; and that even at the great altitude of 20,000 feet the lactic acid was barely above the normal level. Dill (19) states

that while these findings at present cannot be explained the fact that the blood lactate is not elevated at high altitudes presumably serves as a safeguard against overexertion of the body. He points out that, if the body at high altitudes could produce such severe disturbance in the acid-base equilibrium as it can at sea-level, grave injury might be caused.

Finally, Barcroft has stated (6): "The effects of lactic acid increase therefore 'may' take place at high altitudes without any actual increase in the formation of the same." This is an interesting suggestion, and it is indeed difficult to dispute it; but the burden of proof surely lies with its advocates.

The effect of anoxia on the blood sugar.—In 1857 Claude Bernard (9) noticed that the urine of animals which had been poisoned by carbon monoxide contained sugar. Since his original observations this has been verified by many workers. This glycosuria apparently is due to the mobilization of liver glycogen, since it does not occur if the animals have been starved previous to the exposure of carbon monoxide (32). Ziesche (68) in 1908 postulated that diabetes may follow exposure to carbon monoxide asphyxia. This, however, has never been substantiated.

Kellaway (46) in 1919 came to the conclusion that mobilization of sugar during anoxia was caused by the effect of oxygen want on the central nervous system. Although evidence was available that the output of epinephrine was accelerated, he felt that this was not the cause of the increased blood sugar.

In 1926 Mikami (53), working with rabbits, concluded that the increase in blood sugar (and urine sugar as well) was roughly proportional to the degree of anoxia. As a matter of fact, Munzer and Palmer (56) many years before, working with men, had reached the same conclusion. Mikami also showed that intravenous injection of alkali inhibited the hyperglycemia and, further, that it prevented the fall in arterial carbon dioxide associated with carbon monoxide poisoning. His works suggest that the acid-base balance of the blood may play an important part in the production of hyperglycemia.

Messerle (52) in 1928 reported observations of an indeterminate nature on the effects of the climate of high altitude on blood sugar of

man during the first few days' sojourn and as acclimatization progressed.

In 1933 Buersch (14) reported that rabbits which were exposed daily to carbon monoxide showed an increase in their blood-sugar level. In the same year Boedicker (11), however, reported the opposite findings, namely, that following the administration of glucose by a stomach tube no definite evidence could be found that the form of the blood-sugar curve was altered after the animals were subjected to repeated exposures of carbon monoxide.

Schulze (60) in 1936, working with mice and using carbon monoxide to produce anoxia, concluded that the adrenals were stimulated by asphyxia and that they were responsible for the immediate rise in blood sugar. His view, then, was opposed to that of Kellaway.

The effect of complete anoxia on the blood sugar of the turtle has been reported by Johlin and Moreland (43). Turtles which were very resistant to anoxia were kept in an atmosphere of pure nitrogen up to 28 hours. The glucose rose from 50 mg. to 1,200 mg. In a subsequent paper (54) it was reported that alkali lowers the high blood sugar produced by complete anoxia in the turtle but causes a further increase in the lactate, so that there is a reduction of the sugar-to-lactate ratio. This finding confirmed, in part, the previous work of Mikami (53).

Gellhorn and Packer (26) have reported studies on the glycogenolytic action of epinephrine. They observed that short periods of anoxia (7 per cent oxygen) acted antagonistically to insulin hypoglycemia, whereas prolonged periods (2 hours) aggravated hypoglycemia. The glycogenolytic action of epinephrine during a short period of anoxia was increased, but was lost after a prolonged period; this presumably was not due to depletion of the glycogen reserves of the liver.

Forbes (24) in 1936 reported observations on blood sugar and glucose tolerance at high altitudes up to 6,140 meters (20,144 feet) in acclimatized subjects in rest and at work. At 5,340 meters (17,520 feet) glucose-tolerance tests were given. Although the blood sugar rose slightly with altitude, there was no conclusive proof that high altitudes caused it, and during work the behavior of blood sugar was

approximately the same at all altitudes. In two of three subjects the glucose tolerance was greatly decreased at 5,340 meters.

In 1938 Glickman and Gellhorn (28) subjected rats that had received insulin to mild degrees of oxygen want (barometric pressure of 460 mm. Hg [13,000 feet]). The insulin convulsions showed a greater severity and shortened latent period than they did at atmospheric pressure. The blood-sugar level apparently was not affected by the anoxia. Glickman and Gellhorn's interpretation was that the low blood sugar interfered with the oxygenation of the central nervous system, so that if an animal with a low blood sugar be subjected to a mild degree of anoxia a picture is created which resembles acute anoxia.

McQuarrie and Ziegler (50) in 1939, working with dogs, reported results which were not in accord with those of Glickman and Gellhorn, previously mentioned. They found that anoxia prevented insulin convulsions in spite of the fact that the blood-sugar level in insulinized dogs subjected to anoxia was lower than in those animals treated with insulin alone. In a subsequent paper Gellhorn *et al.* (27) confirmed the work of McQuarrie and Ziegler and came to the conclusion that in all species thus far studied anoxia prevented insulin convulsions. Gellhorn and his co-workers explained that the convulsions produced in insulinized rats which were subjected to anoxia were of an anoxic, rather than of a hyperglycemic, nature. They regarded this specific sensitivity of anoxia as characteristic of small animals, which are known to have a high metabolic rate.

To summarize the effect of anoxia on blood sugar, it may be said that, while there appears to be considerable evidence that oxygen want produces a rise in the blood-sugar level, more well-controlled work is needed on both normal unanesthetized animals and man.

Nonprotein nitrogen.—Armstrong and Heim (3) exposed animals to simulated altitudes of 18,000 feet daily for 4 hours, and no change was noted in the nonprotein nitrogen of the blood. This, too, seemed to hold true for human beings, since the work was repeated on men, but at lower levels (12,000 feet), and no change was noted.

Sodium chloride.—Armstrong and Heim (3), using the same procedure as they did when the nonprotein nitrogen was studied, found that anoxic anoxia apparently had no effect on the amount of sodium

chloride in the blood. It was found by Sundstroem (63) that at the beginning of residence at high altitudes there was a definite initial reduction in the excretion of chlorides.

Potassium.—It has been shown by several authors (15, 18, 40, 55, 69) that a generalized asphyxia of an animal causes a stimulation of the adrenals and a liberation of potassium. Mullin *et al.* (55) reported an increase in the blood potassium in tetany and in asphyxia in dogs. They could not account for the increase on a basis of loss of blood fluid or a potassium shift from the red blood cells to the plasma. The interpretation was that it came from active muscle tissue or from the liver. It was suggested that the elevated potassium level might serve to increase the irritability of the central nervous system and synaptic conduction during asphyxia.

Cattell and Civin (15) in 1938 found in the cat that 4–5 minutes of complete asphyxia caused a rise in blood potassium to 38 mg. per 100 cc. (normal range is from 10 to 30 mg. per 100 cc.). This returned to normal within 2 or 3 minutes after normal respiration was resumed.

In 1936 Houssay and his co-workers (40, 41) reported that the potassium rise produced by asphyxia could be eliminated by sectioning the splanchnics or by performing either adrenalectomy or hepatectomy. They reported further that anemia, produced by stimulating the peripheral end of the vagus until the heart stopped, produced a rise in blood potassium and that hemorrhage did likewise. The rise in blood potassium produced by hemorrhage could be prevented only by hepatectomy. They concluded that the asphyxia stimulated the adrenals to secrete more epinephrine and that this caused the liver to mobilize the potassium.

Fenn (22) has pointed out that it is not certain that all the potassium comes from the liver, since a loss due to asphyxia has been reported in the heart (16, 17) and in the skeletal muscle in the cat (4, 23). He feels that, while probably all the tissues tend to give up some potassium during asphyxia, most comes from the liver as a result of a specific adrenalin mechanism.

While considerable work has been reported on the effects of asphyxia on the potassium level in the blood, there have been relatively few reports of the influence of anoxic anoxia on this substance.

Sundstroem (63), a number of years ago, found that at high altitudes there was an increase in the excretion of potassium. Hall *et al.* (31) reported that when rabbits were transported to high altitudes the blood potassium was greatly reduced; that of the llama, however, was but slightly reduced. The authors pointed out that the animals were excited when the control blood samples were taken at sea-level. This was unfortunate, since true normal values might not have been obtained. It was reported by McQuarrie and his co-workers (51, 67) in 1940 that dogs which had been allowed to breathe 5–9 per cent oxygen in nitrogen for several hours showed a decrease in the plasma potassium.

It appears, then, that, while asphyxia causes an immediate increase in the blood-potassium level, anoxic anoxia, especially if somewhat prolonged, may cause a decrease. Further studies are obviously needed on this problem.

Guanidine.—Andes *et al.* (1) found no change in the level of guanidine in the blood in dogs after exposure to a simulated altitude of 24,000 feet (barometric pressure 294.4 mm. Hg) for periods up to $7\frac{1}{2}$ hours. Short exposures ($\frac{1}{2}$ hour) at 28,000 feet (barometric pressure 246.8 mm. Hg) likewise had no effect.

Bilirubin.—Bilirubin is somewhat increased in the blood because of increased destruction of the red cells, as shown by Hurtado (42), who made determinations on twelve normal native Peruvian Indians. He used Van den Bergh's indirect method. It has been pointed out by Verzar that this is a useful adaptation, since bilirubin is thought to stimulate red blood cell formation. It should be mentioned, too, that Hurtado also found a small amount of urobilin in the urine.

Tanaka and Homma (65) in 1936, working with rabbits, reported that severe degrees of anoxia (corresponding to 5,000 meters and more) produced a decrease in the excretion of bilirubin.

The effect of anoxia on blood lipids.—As far as the author is aware, the effect of oxygen want on blood lipids has not been reported in man; for the main part, work of this nature has been performed on rabbits.

A number of workers (13, 33, 39, 61, 62) have shown that anemic anoxia, that is, hemorrhage, produces a lipemia. It is generally

agreed that the increase in blood lipids is confined to the plasma. In 1920 Horiuchi (39), working with rabbits, showed that a single acute hemorrhage (45 cc.) or repeated bleeding results in a marked lipemia; return to normal values required a period of from 14 to 18 days.

Sundstroem and Bloor (64) in the same year reported that short exposures to atmospheric pressures from 350 to 400 mm. Hg (20,000–17,000 feet) caused an average decrease in plasma phospholipins of 13.2 per cent. It was thought that the decrease was due to an enrichment of the erythropoietic organs, that is, a redistribution of phospholipins from the blood-forming organs.

Schmensky (59) found that blood cholesterol increased at high altitudes. Whereas normally it is found in the blood at a concentration of 180 mg. per cent, at Davos (5,100 feet) he found it to be elevated to 200 mg., and in some natives from 350 to 480 mg. per cent. The cause of this rise is not clear; the intense sunlight at high altitudes may play a part. Schmensky has shown that hypercholesteremia may develop in a dog which has been exposed for long periods to strong sunlight. Guzman-Barron (8) claims, however, that hypercholesteremia does not occur in acclimatized inhabitants in the Andes. Hurtado (42) reached the same conclusion.

The experimental work reported by Starup (62) in 1934 is of especial interest. Working with rabbits, he found that a hemorrhage of one-fifth to one-sixth of the blood volume produced a lipemia which involved all the blood lipids; neutral fat was affected the most; cholesterol next; and lecithin least. A marked lipemia was found to result from the administration of phenylhydrazine, from the intravenous injection of distilled water, or from exposure to a reduced barometric pressure of from 300 to 360 mm. Hg (24,000–19,000 feet). He concluded that the immediate cause of the lipemia was due to reduced oxygen tension both when the atmospheric pressure was reduced and when anemia was produced by the various methods.

MacLachlan (48) in 1939 showed that there is a wide variation in different animals in their response to oxygen want as far as blood lipids are concerned. The blood-plasma lipids of cats and dogs exposed to oxygen want for short periods were not affected either during the fasting state or during the active absorption from the intestine. In the rabbit, however, there was a fall in plasma lipids after 3

hours of anoxia (254 mm. Hg), and normal levels were established in 6 hours; this fall was due to a decrease in neutral fat content mainly. It was suggested that the difference in response of the rabbit from that of the dog and cat might be due to different abilities to utilize fats.

Since rabbits do not respond like other mammals studied, it is not permissible to draw conclusions concerning the possible effect of oxygen want on the blood lipids in man. This phase of the work deserves further study.

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EFFECT OF ANOXIA ON THE HEART AND CIRCULATION

EFFECT OF ANOXIA ON THE HEART RATE

1. *Acute effects.*—It is well known that acute anoxia produces an acceleration of the heart beat. It was shown by Lutz and Schneider (54*) that if subjects were allowed to breathe pure nitrogen an acceleration of the heart within 5–55 seconds (in 66 per cent of all cases within 15 seconds or less) would be observed. Experiments by the same authors performed in a low-pressure chamber, in which the barometric pressure was lowered at a rate corresponding to an ascent of 1,000 feet a minute, showed a quickening of the pulse in 26 per cent of all subjects at tensions of oxygen equivalent to an altitude of 4,000 feet or less. Hodgson (42) in 1919, making observations in airplane flights at 16,000 feet, found typical low-oxygen action well illustrated.

Greene and Gilbert (28) in 1922, working with dogs and using a rebreather to produce anoxia, found that the respirations became more and more rapid until a critical point was reached, beyond which the respiratory center showed signs of failure. The authors called this the "respiratory crisis." For the main part, in the type of anoxia which they established, the pulse followed the respiration; but after the respiratory crisis was reached, the heart began to fail.

Barcroft (4) has pointed out that in the resting animal anoxia produces cardiac quickening until the central nervous system commences to lose its grip. It is not known how much of this effect is due to loss of vagal tone or to increase in sympathetic control. He has stated, further, that, without doubt, altitudes above 10,000 feet quicken the pulse in unacclimatized individuals at rest.

Experiments by Schneider and his co-workers (76) have shown that the heart rate slowly and gradually increases until the oxygen tension is equivalent to that of about 14,000 feet (446 mm. Hg barometric pressure). After this altitude has been reached, the heart rate increases by much greater increments for each 1,000 feet of

* See p. 97 for bibliographical references.

ascent; at 15,000 feet (428.8 mm. Hg) the increase averaged 15 beats; and at 18,000 feet (379.4 mm. Hg), 20 beats.

Recently McFarland (55) has reported that in an ascent by train from sea-level to an altitude of 14,890 feet six subjects showed an increase in the basal pulse rate from an average of 65 beats to 75.7 beats. In the standing position there was an increase from 78.3 to 89.5 beats. In an airplane flight of 50 minutes' duration, starting at sea-level and reaching an altitude of 15,000 feet, observations on four subjects showed a distinct increase in pulse rate in all; in one subject the pulse rose from 60 to 98 beats per minute; in a second subject from 100 to 116; in a third from 68 to 86; and in a fourth from 72 to 115. It may well be, however, that excitement contributed somewhat to the increased pulse rate.

Wright (94) states that anoxia, by stimulating the accelerator center, produces first an increase in the frequency and in the apparent force of the heart beat. Since, by this means, the blood is kept moving more rapidly, he regards this as an adaptive measure. He suggests further that the force of the heart beat dies down later but that the increased rate may continue.

It has been shown by several workers (31, 54, 71) that, if the constant level of low oxygen tension be maintained for an hour or more, the rate is retarded in many instances, but in some cases the augmented rate continues.

2. *Chronic effects.*—It is known that if a person who is in good physical condition ascends passively to an altitude of 14,000 feet there may be no increase in pulse rate. Schneider (72) points out, however, that after several hours the pulse is apt to accelerate and may continue to do so for the next 3–5 days. If the person suffers from mountain sickness, there is a pronounced acceleration of the heart rate; but as the attack wears off, this subsides. It is generally agreed that the greatest augmentation of the heart rate occurs in those who are not in good physical condition.

According to Schneider, there is a good deal of individual variation at 14,000 feet; some subjects show but a slight increase in cardiac rate, while in others there is a rise of 10 beats or more. He and his co-workers (75) did not find the pulse extraordinarily labile at high altitudes, and they further found that the heart works at an in-

creased rate in all postures, with about the same differences as at low altitudes. If a prolonged sojourn is made at high altitudes, there may be a daily increase of cardiac rate for a week or two, but the tendency is for the rate to return toward the low altitude rate (14) as other adaptive changes reach their maximum efficiency. Only rarely, however, does the pulse rate return to normal.

3. *Effects of anoxia on the heart rate in acclimatized subjects.*—After a degree of acclimatization has been reached, anoxia has not the same effect on the heart as it did before this took place. The early literature on this subject has been reviewed by Durig (18) and by Schneider and Sisco (74).

TABLE 6

PULSE IN CHAMBER AT REDUCED PRESSURE: THE EFFECT OF REDUCED BAROMETRIC PRESSURE ON PULSE RATE IN AN UNACCLIMATIZED INDIVIDUAL*

Pressure (Mm. Hg)	Approximate Altitude (Feet)	Pulse per Minute
720	1,500	64
650	4,000	72
424	15,000	84

*Modified from Starling's *Human Physiology* (7th ed.; Philadelphia: Lea & Febiger, 1936), p. 916.

It is generally agreed by all workers that acclimatized inhabitants living at elevations from 8,000 to 9,500 feet show no altitude augmentation of heart rate. Barcroft (4) states that there is no evidence that altitude up to 14,000 feet quickens the pulse. He points out that our knowledge is rather meager concerning pulse rate beyond 14,000 feet, but he feels that each individual would probably reach a point where the pulse would be increased. A critical altitude for one person, however, would be different from that for another. He calls attention to the data of Major Hingston, medical officer to the Mount Everest Expedition of 1924 (41), which give the pulse rate of one individual at various altitudes (see Table 7).

One of the most interesting points shown by the data of Hingston is that the pulse rate per minute while sitting showed no acceleration until an altitude of over 16,500 feet was reached. To Hingston's data

may be added the observations of Norton (41), whose pulse was normally 40 and when resting at the great altitude of 27,000 feet was only 60. Monge (65) observed that the Peruvian natives living at altitudes of 12,000 and 14,890 feet showed a tendency toward bradycardia; in over 12 per cent of those examined he found a resting pulse between 40 and 60 beats per minute.

4. *Aftereffects of anoxia on the heart rate.*—The aftereffects of anoxia on heart rate are different from those of respiration (p. 112). They depend upon the length of time the individual has been ex-

TABLE 7

THE PULSE RATE OF ONE INDIVIDUAL AT VARIOUS ALTITUDES*

ALTITUDE (FEET)	PULSE RATE PER MINUTE		
	Sitting	Standing	After Regulated Exercise
Sea-level	72	72	84
7,000	72	84	96
14,300	72	84	108
16,500	72	96	120
21,000	108	120	144

* From data of Major Hingston in J. Barcroft, *The Respiratory Function of the Blood* (Cambridge University Press, 1925), Part I, "Lessons from High Altitudes," Appen. I, p. 182.

posed to anoxia; if he has been exposed only for an hour or so, the heart returns to its normal rate at once; if, however, the sojourn at high altitudes has been long enough for acclimatization to take place, upon the subject's return to a low altitude the cardiac rate may be subnormal for many days, as has been shown by a number of workers (18, 36, 70, 83).

5. *Effect of exercise on the pulse rate at high altitudes.*—The effect of exercise upon the pulse rate at high altitudes depends upon whether or not acclimatization has taken place. In the nonacclimatized individual relatively mild exercise will produce the same symptoms at high altitudes as will severe exercise at low altitudes, namely, a forcible and rapidly beating heart with concomitant breathlessness.

As would be expected in the acclimated subject, exercise at high altitudes does not speed up the heart as it does in the unacclimated. The data of Hingston (Table 7) show, however, that even in the acclimated subject exercise at high altitudes produces a rapid heart. Somervell (79), a member of one of the Mount Everest expeditions, reported that while climbing at an altitude of 27,000–28,000 feet his heart was beating from 160 to 180 beats per minute. He described it, however, as being in good rhythm and of good volume. It is hardly necessary to point out that an unacclimatized subject probably could not live at such an altitude.

THE EFFECT OF PROGRESSIVE ANOXIA ON THE HEART AND THE CIRCULATION

Several workers (23, 24, 28, 69, 72, 77, 91) have studied the effect of progressive anoxia on the heart and circulation. These studies have shown, for the main part, that under those conditions the heart accelerates, the systolic pressure is either maintained or gradually falls, and the pulse pressure remains unchanged or increases.

One study that reported on the effect of progressive anoxia on the heart and circulation, which is of especial interest here, is that made by Sands and De Graff (69) under the direction of Dr. Carl Wiggers. Working with dogs, these investigators came to the conclusion that anoxia improved the circulation and helped supply the tissues with oxygen until the oxygen in the inspired air reached 9 per cent; when the oxygen percentage was diminished below this point, a circulatory crisis occurred.

They pointed out that anoxia has two opposing effects on the heart. On the one hand, it produces a reduction in the effective venous pressure, which reduces cardiac filling, and it also produces an abbreviation of the systolic phase of ejection. On the other hand, anoxia raises the initial tension in the left ventricle and also increases the velocity of ventricular ejection. These two opposing factors during the course of the early stages of progressive anoxia remain evenly balanced and tend to maintain or increase slightly the normal systolic discharge.

They account for an increase in the minute flow of the blood through the body during anoxia as being due to (1) an increased

systolic discharge, (2) an increased rate of heart, and (3) a reduced peripheral resistance. This beneficial influence of anoxia, however, persists only until the concentration of oxygen reaches 9 per cent; then a circulatory crisis occurs. There is first a decline of systolic and diastolic pressures and a reduction in pulse pressure. Beginning signs of failure of the circulation become manifest owing to a reduction in the minute output of the heart. The heart becomes slower, the ejection phase becomes still more abbreviated, and circulatory collapse becomes imminent, since the combination of these factors causes the cardiac output steadily to diminish; soon the blood pressure drops to a point incompatible with the life of the animal.

These workers state that there is some evidence that the stimulating effects of anoxia up to the point of the circulatory crisis (which occurs at 9 per cent oxygen) may be accounted for by the fact that anoxia either depresses the vagi or stimulates the accelerator mechanism. When the vagi are cut, the cardiac acceleration produced by anoxia is often, but not always, absent, indicating that the accelerator mechanism may be stimulated.

Wiggers (92) recently has reviewed the effect of progressive anoxia on the heart and circulation and points out that most laboratory investigators (13, 29, 43) have concluded that oxygen lack has no stimulating action on the ventricles and that dilatation and depression result when blood is about one-half saturated with oxygen. His views are not in accord with this concept, and he calls attention to the work of Sands and De Graff, previously mentioned, and to that of Strughold (84). This last-named investigator worked with dogs with a "controlled circulation" (i.e., animals with heart rate, arterial diastolic pressure, venous pressure, and alveolar carbon dioxide kept constant). He used a cinematographic method for recording changes in heart size during successive movements of the heart cycles and found that gas mixtures which contained less than 10 per cent oxygen produced the following: (1) an increase in diastolic volume (independent of changes in the venous pressure), (2) increased systolic discharge, and (3) an increase in systolic and pulse pressure (when diastolic pressure was kept constant).

Wiggers also calls attention to the fact that during anoxia the ventricles eject the blood with a greater economy of effort, as judged

by a criterion published from his laboratory in 1928 (93) and which recently has been corroborated on the human subject (21). He has summarized the effects of progressive anoxia on the heart and circulation as follows: A progressive decrease in respired oxygen volumes to about 12 per cent (which period he calls *hypoxia* and which corre-

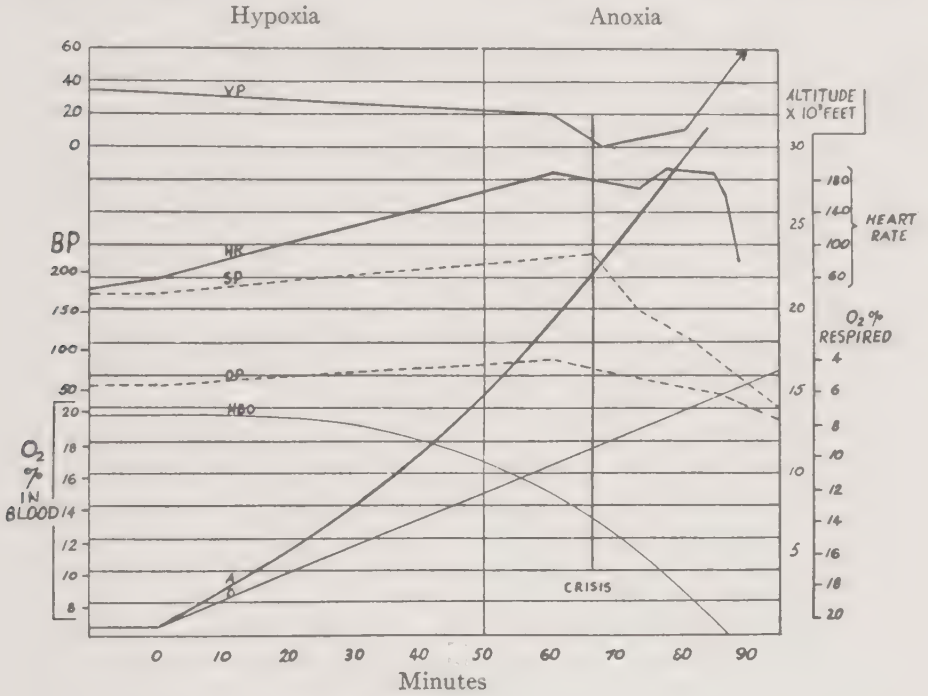

FIG. 8.—The effect of progressive anoxia on the heart and circulation. Graph showing relation of percentage of oxygen respired (*O*) to altitude (*A*) and oxygen saturation of blood (*Hb*) and division into stages of hypoxia and anoxia. Smoothed curves showing trend of reactions of venous pressure (*VP*), heart rate (*HR*), systolic (*SP*) and diastolic (*DP*) pressures in dogs during progressive hypoxia and anoxia. (From Wiggers, *Annals of Internal Medicine*, 14, 1239, 1941.)

sponds to blood oxygen saturation to about 75 per cent and to altitudes to 15,000 feet) increases the flow of blood by redistribution of blood flow and by cardiac acceleration. He attributes the increased cardiac rate to decreased vagal tone, to increased accelerator nerve activity, and perhaps to some direct effect on the S-A node. During this period the vigor of ventricular contractions increases, the period of systolic expulsion shortens, and the effective venous pressure falls slightly.

When the oxygen in the inspired air falls below 12 per cent (which he calls the "true period of anoxia"), a greater stroke volume occurs, there is a further increase in velocity of ejection, and the economy of effort is enhanced. When the oxygen declines to 7 or 6 per cent, which corresponds to an arterial-blood oxygen saturation between 50 and 35 per cent and to altitudes up to 30,000 feet, a coronary crisis occurs. The arterial pressure declines abruptly, the pulse pressure is reduced, the systolic pressure decreases, the venous pressure rises greatly, and various types of conduction and rhythm disturbances may occur. Wiggers feels that the circulatory crisis is essentially an acute congestive heart failure due to the depressant effect of anoxia on the myocardium.

THE EFFECT OF ANOXIA ON CARDIAC OUTPUT

Numerous investigations with discordant results have been made concerning the effect of anoxia on cardiac output.

Observations on cardiac output by the Anglo-American Pike's Peak Expedition in 1911, by means of a recoil board and measurement of pulse pressure, showed that the volume of the heart strokes continued practically the same on Pike's Peak as at low altitudes. In 1916 Hasselbalch and Lindhard (35), working with a low-pressure chamber at a simulated altitude of somewhat less than 12,000 feet and using a respiratory nitrous oxide method developed by Krogh and Lindhard, came to the conclusion that the output of the heart was not increased at high altitudes during rest. In 1913 Kuhn (49), working at an altitude of 11,000 feet and using the respiratory method of Plesch, obtained indeterminate results in four individuals.

Lutz and Schneider (54) in 1919 concluded from experiments performed in a low-pressure chamber that there was an increased cardiac output during anoxia. In 1921 Doi (13) found, however, that the volume of blood passing through the lungs during acute anoxia in an unanesthetized cat was the same as under ordinary atmospheric pressure. By working out the minute volume, he calculated that the output of each heart beat had decreased. His work indicated that the acceleration of the heart in anoxia is a symptom of distress.

In 1924 Schneider and Truesdell (77), using the rebreather method to induce anoxia, came to the conclusion that the cardiac out-

put was not increased during anoxia and at times might be decreased. They concluded further that the circulatory changes in anoxia do not serve as a means of compensating for a lack of oxygen but rather that they should be interpreted as signals of distress. Sands and De Graff (69) in 1925 found, however, that during progressive anoxic anoxia there was an increase in cardiac output and an increase of the minute flow of the blood until the oxygen percentage reached 9, at which point the opposite became true.

Dreyer (15) in 1926, working with a cardiometer on decerebrate cats, found that anoxia which lowered the arterial oxygen saturation from 50 to 80 per cent caused an increase in cardiac output. Kirsch (47) in the same year, using overventilation in curarized dogs so as to produce an arterial oxygen saturation of 70 per cent, also found an increase in cardiac output. Jarisch and Wastl (43) in the same year found that, when the arterial blood was less than 60 per cent saturated, cardiac dilatation ensued and the output was diminished. Their work was done on urethanized animals, and vagotomy and thoracotomy had been performed. Gremels and Starling (29), also in the same year, working with a heart-lung preparation, found that anoxemia first produced no change and then a diminution in the systemic output of the heart.

Harrison and his co-workers (34) have criticized the results of the investigators who have reported that anoxia decreased cardiac output, on the grounds that their observations were made mostly on anesthetized animals and that nearly all work involved thoracic operations which entailed shock. The studies which have been reported on man were concerned with blood flow in only one part of the body, or indirect and unreliable methods were used.

Harrison and Blalock (32) in 1927 showed that severe anoxic anoxia of short duration caused an increase in the minute cardiac output. It was also shown that a rapidly produced anemia led to increased cardiac output. The work suggested that the minute cardiac output might be inversely proportional to the tissue oxygen tension. If the arterial blood was less than 70 per cent saturated with oxygen, the minute cardiac output was always increased. In the same year Harrison *et al.* (34), using the Fick method, found that cardiac output in normal unanesthetized dogs first showed an increase when the

arterial blood was saturated about 75 per cent. They designated this the "anoxemia threshold."

In a later paper (33) the conclusion was reached that the circulatory response to anoxic anoxia was independent of the nervous system and endocrine glands but was due to a vascular action. They also produced some evidence which indicated that the tension of oxygen in the heart muscle was possibly the most important factor in the control of the circulatory minute volume.

Harrison and his co-workers (34) definitely felt that, if the oxygen saturation fell below 75 per cent, cardiac output increased. In support of their views they pointed out, first, that their findings have been uniform throughout their work, which is in contrast to that of other workers; second, that the Fick method which they employed to determine cardiac output is conceded to be very accurate; and, lastly, that they used normal unanesthetized animals which had suffered no operative manipulations.

More recent investigations have corroborated the findings of Harrison and his co-workers. The work of Strughold (84) has been mentioned previously (p. 78). Grollman (30) in 1930 made observations on two subjects on Pike's Peak. He reported that the heart output per minute increased steadily for about 4 or 5 days, reaching a maximum of about 48 per cent above its sea-level value, and then gradually declined to its normal level as the hemoglobin concentration was increased. Christensen (10) in 1937 reported observations made on the cardiac output of members of the Chilean Expedition. His work agreed qualitatively with Grollman's, but quantitatively he did not find the same relations between circulatory rate and hemoglobin concentration as did Grollman.

It is now generally accepted that anoxic anoxia, within certain ranges, produces an increase in cardiac output, and some investigators feel that this plays an important role in the ability of an individual to withstand anoxia and to become acclimatized to high altitudes (10, 12, 30, 37, 59, 60).

THE EFFECT OF ANOXIA ON BLOOD-VOLUME FLOW

A few workers have reported experiments which deal with blood-volume flow during anoxia. In 1914 Schneider *et al.* (75), working

on Pike's Peak and using Stewart's method for measuring the amount of blood flow through the hand (by determining the amount of heat given off in a water calorimeter), found the circulation rate through the hands in six individuals to be increased from 30 to 76 per cent. These observations, along with experiments on cardiac output, led these investigators to the conclusion that the circulation during anoxia was, as a whole, more rapid.

In experiments performed a few years later, however, Schneider and Truesdell (77), using the rebreather method for producing anoxia, obtained quite different results. They found that the hand volume normally starts to decrease at about 15 per cent oxygen but is more marked after 9 per cent is reached. The blood flow through the hands, as determined by Stewart's hand calorimeter, was decreased in 76 per cent of all tests when the inhaled oxygen was reduced to 13 per cent. In a group of twenty-nine rebreathing experiments at 7 per cent oxygen the mean flow was retarded 32.8 per cent.

Interpretations must be made with care, however, when the blood supply through only one part of the body is studied. Bainbridge (2) has shown, for example, that an increase in blood flow through the hands may be due to a dilatation of the local vessels and may be counterbalanced by vasoconstriction elsewhere, presumably the splanchnic area. Bronk and Gesell (8) in 1926 observed that low oxygen tension caused diminished femoral and increased carotid flow of blood.

It has been mentioned previously that Sands and De Graff (69), in their studies on the effect of progressive anoxia on the heart and circulation, came to the conclusion that there was an increase of the minute flow of blood through the body during anoxia, brought about by three factors: (1) increased cardiac rate, (2) increased systolic discharge, and (3) decreased peripheral resistance. Freeman *et al.* (22) in 1936, however, studying the effects of oxygen deficiency on the peripheral blood flow, obtained variable results. Making similar studies, Gellhorn and Steck (25), using man as a subject and using 7.6–9.8 per cent oxygen mixtures, also reported variable results.

In summary, it may be said that there is need for more well-controlled work on the effect of anoxia on blood-volume flow. With the exception of the spleen, no work has been reported of the effect of

anoxia on blood-volume flow of the abdominal organs. In order to study this problem thoroughly, simultaneous plethysmographic tracings should be taken of various organs of the body, as well as of the limbs, during various degrees of anoxia.

THE EFFECT OF ANOXIA ON THE CORONARY CIRCULATION

In 1925 Hilton and Eicholtz (40) performed experiments which indicated that there was an improved flow of blood through the coronary vessels during anoxic anoxia, so that an increased blood flow through the heart was supplied even though there were no changes in arterial pressure. The results reported by these workers have been corroborated by other investigators (26). It is now known that the volume of coronary flow increases greatly when the oxygen is reduced to 8 or 9 per cent. In point of fact, it has been shown (44) that anoxia is a more powerful vasodilator of the coronary vessels than preparations such as sodium nitrite, amyl nitrite, histamine, and certain xanthin derivatives. It is, indeed, of great interest that anoxia is capable of exerting such a powerful vasodilator action. It doubtless serves as a valuable compensatory mechanism when the organism is subjected to severe anoxia. In this connection Wiggers (92) has written:

> The pronounced anoxic vasodilatation is doubtless a providential mechanism by which the cardiac pump is sustained so well in progressive anoxia; indeed, it is probable that myocardial stimulation is converted into myocardial depression as soon as the augmentation of coronary blood flow cannot keep pace with the decreasing volume of oxygen carried by the blood.

THE EFFECT OF ANOXIA ON THE CONDUCTION OF THE NORMAL CARDIAC IMPULSE

Early electrocardiographic studies (19, 28, 61, 62) were reported which indicated that anoxic anoxia delayed the conduction of the normal cardiac impulse. In a series of papers in 1925 Resnik (67) reported that studies made on dogs which had been subjected to anoxic anoxia suggested that the S-A node was highly sensitive to anoxia and that there was a brief period in which impulse formation was accelerated, but that this period was rapidly followed by a progressive slowing of the intrinsic rate of the heart. Anoxia, furthermore, first produced a shortening and later a lengthening of the A-V con-

duction; intraventricular conduction, however, was only slightly affected. Resnik believed that the changes in conduction were brought about by anoxia directly affecting the myocardium.

It is known that moderate degrees of anoxia may produce a vagospasm (19, 89); and doubtless this could, in part, account for the delayed conduction. Severe degrees of anoxia probably produce a delayed conduction by directly affecting the conduction tissue.

THE EFFECT OF ANOXIA ON ELECTROCARDIOGRAPHIC TRACINGS

The most common finding with the electrocardiogram under anoxic conditions is that the T wave is either decreased or inverted. During severe degrees of anoxia there may be a slowing of the conduction rate, as evidenced by the lengthening of the P-R interval, that is, the time it takes the impulse to travel from the S-A node to the A-V node. At times there may be other changes in the electrocardiographic tracing, such as a deformity of the QRS complex. It has been reported by a number of investigators (46, 51, 68) that normal individuals who had been subjected to a generalized anoxemia showed an S-T deviation in their electrocardiogram.

ANOXIA AND CARDIAC DILATATION

It has been known for some time that severe degrees of anoxia may cause cardiac dilatation. In 1917 Kaufmann and Meyer (45) clinically studied the hearts of soldiers who had returned from campaigns in mountainous districts and found these hearts greatly increased in size. Whitney (91) in 1918, working at Mineola, found that, of ten medical officers subjected to anoxia by use of the rebreather, five showed noticeable cardiac dilatation, as ascertained by percussion—one corresponding to an altitude of 14,000 feet, one to 16,000 feet, two to 18,000 feet, and one at 20,000 feet. Le Wald and Turrell (52) in 1920, working with aviators and using the x-ray, could find no pronounced cardiac dilatation. On the Peruvian Expedition in 1922, Barcroft *et al.* (5), using the x-ray at 14,000 feet, found no cardiac enlargement and in several cases found the heart smaller than at sea-level. Somervell (79) in 1925 reported that all the men who went higher than 27,000 feet had dilated hearts, recovery from which required 1–3 weeks.

The fact that anoxia may produce cardiac dilatation has been verified experimentally on animals by a number of workers (29, 43, 69, 85, 86).

It is of interest that some of the investigators reported that the heart was smaller during anoxic conditions. This may be explained by the fact that the cardiac rate was increased above the normal (63).

Since Starling and his co-workers (80) have shown that the energy of contraction is a function of the length of the muscle fiber, it is not illogical to interpret moderate cardiac dilatation at high altitudes as an adaptive mechanism. The fact, too, that there is an increased cardiac output under anoxic conditions also favors this view. There is reason to believe, however, that in the normal heart there is an increased cardiac output under anoxic conditions before noticeable cardiac dilatation may be manifested.

Pronounced dilatation (such as is seen in the terminal stage of acute anoxia) is known, however, to reduce greatly the efficiency of the heart. It may be that even moderate cardiac dilatation produced by anoxia is a signal of distress.

ANOXIA AND CARDIAC HYPERTROPHY

Strohl (81) in 1910 reported that the heart-weight/body-weight ratio of the alpine snowbird (*Lagopus alpinus* Nilss), which inhabits high altitudes, was much greater than that of the near relative, the moor snowbird (*Lagopus albus* Gmellin), which lives at lower levels. He drew the conclusion that the greater heart weight in the former was due to two factors, namely, a work hypertrophy and a specific adaptation to the rarefied atmosphere. In 1912 Strohl (82), and in the same year Meyer (67), using the electrocardiographic method, found a hypertrophy of the right ventricle at high altitudes.

Campbell (9) in 1932 found that mice which had been exposed to chronic carbon monoxide poisoning for a period of 9 months showed a definite cardiac hypertrophy. He thought this was brought about by the increase in viscosity of the blood owing to the increase in red blood cells.

In 1936 Van Liere (87) reported experimental work performed on guinea pigs that had been kept in a low-pressure chamber from 20 to 105 days at barometric pressures ranging from 446 to 380 mm. Hg,

corresponding to simulated altitudes from 14,000 to 18,000 feet. The average heart-weight/body-weight ratios in the animals increased 55.8 per cent above the normal. It was concluded that the cardiac hypertrophy could have been caused either by a work hypertrophy, by a specific adaptation to anoxia, or by a combination of both factors.

It is believed by some (39) that cardiac hypertrophy is associated with acclimatization. No reports could be found in the literature, however, giving quantitative data of the size of the hearts of inhabitants at high altitudes. More work is needed to throw light on this particular point.

Since cardiac dilatation may occur at high altitudes, the development of cardiac hypertrophy would not be unexpected. There are also two factors obtaining at high altitudes which favor the production of cardiac hypertrophy since they throw an additional load on the heart, namely, the increased cardiac rate and the increase in blood viscosity.

Some physiologists feel, however, that cardiac hypertrophy can take place only after the muscle fibers have been stretched beyond their physiologic limit or have suffered other injuries. If this hypothesis is accepted, then the cardiac hypertrophy produced by high altitudes would have to be explained on the grounds that the added strain on the heart produced excessive dilatation. In the past few years, however, a great deal of experimental work has been reported to show that moderately severe exercise may produce cardiac hypertrophy in the normal animal.

Since anoxia can produce cardiac hypertrophy and exercise can produce it also, it would be expected that moderately severe exercise under anoxic conditions should produce a marked hypertrophy. With this thought in mind the author (88) attempted to produce experimental cardiac hypertrophy in guinea pigs by making them exercise in an appropriate cage, which was placed in a low-pressure chamber. The attempts to produce cardiac hypertrophy, however, were unsuccessful. These experiments should be repeated on dogs.

The problem of cardiac hypertrophy under conditions of anoxia is of more than academic interest. A hypertrophied heart is thought to be a weakened one, and any light thrown on the causation of cardiac hypertrophy is of significant interest.

EFFECT OF ANOXIA ON THE BLOOD PRESSURE

ACUTE EFFECTS OF ANOXIA ON THE ARTERIAL PRESSURE

It has been known for many years that acute anoxia produces a rise in arterial blood pressure. This phenomenon is frequently spoken of as "an asphyxial rise." It will be recalled, however, that the term *asphyxia* should be used only when there is an actual increase in the carbon dioxide content in the blood and in the tissues; if there is no accumulation of carbon dioxide during oxygen want, the condition is termed *anoxia*.

The cause of rise of blood pressure during acute anoxia.—In 1930 it was shown by Heymans *et al.* (38*), working with dogs, that whereas inhalation of nitrogen caused the usual rise of blood pressure in the intact animal, if the nerves to the carotid sinuses were severed and the vagi, too, were cut, anoxia produced by the inhalation of nitrogen caused a fall in blood pressure. Selladurai and Wright (78) in 1932, however, reported that after complete elimination of the chemoreceptor nerves oxygen deficiency produced a variable effect on the blood pressure. Von Euler and Liljestrand (20) in 1936, working with intact anesthetized dogs, found that 8.5 per cent oxygen caused a slight rise in blood pressure but that after denervation of the carotid sinus the same degree of anoxia caused a fall. These authors felt that in the experiments reported by Selladurai and Wright complete denervation had not been performed. Brewer (7) in 1937 found that nitrogen inhalation in an animal which had its sinus denervated produced a fall in blood pressure, thus confirming work reported by previous investigators. Bernthal (6) in 1938 recognized the importance of controlling respirations, as well as other experimental procedures, when working on reflexes from the carotid sinuses. After performing some carefully controlled experiments he reported that if the chemoreceptors in the carotid bodies were stimulated either by anoxia or by carbon dioxide excess a vasoconstrictor reflex was produced; the first mentioned method of stimulation, however, gave the most effective result.

* See p. 97 for bibliographical references.

Gellhorn and Lambert (24) felt that further well-controlled experiments were necessary in order to determine the role of the chemoreceptors in the blood-pressure reactions to oxygen deficiency and carbon dioxide excess. They believed that respiration should be rigidly controlled and wrote as follows: "If it is true that pure anoxia and asphyxia are fundamentally different in their action on the isolated vasomotor center, a prerequisite for adequate investigations must be the complete control of the respiratory volume, i.e., artificial respiration."

They performed extensive and carefully controlled experiments on dogs. (For details of their experiments the reader is referred to their monograph on this subject [24].) They came to the conclusion that "oxygen deficiency causes a rise of blood pressure only by action on the carotid and aortic bodies, which in turn send afferent impulses to the vasomotor centers through the carotid sinus nerves and the aortic nerves. . . . ." They further pointed out that the vasomotor center actually was depressed by oxygen want after denervation of the chemoreceptors and that in this regard it behaved very much like the respiratory center during oxygen want.

Cause of the fall of blood pressure produced by oxygen want after denervation of the chemoreceptors.—Gellhorn and Lambert (24) have offered three possible reasons for the fall of blood pressure caused by oxygen want after denervation of the chemoreceptors: (1) a depression of vasomotor tone, (2) a decrease in cardiac output, and (3) a peripheral vasodilatation. These authors felt that under the conditions of their own experiments the first-named factor was the cause for the reversal of blood pressure. It should be pointed out, however, that the second-named cause, that is, a decrease in cardiac output, is active only during severe degrees of anoxia, since it has been shown clearly that it is only under these conditions that the cardiac output decreases.

The effect of small amounts of carbon dioxide on the blood pressure during acute anoxia.—Raab (66) in 1931, working with decerebrate cats, showed that the combined action of carbon dioxide and low oxygen tension had a potentiating effect on the rise in blood pressure. Gellhorn (23) and Gellhorn and Lambert (24, 50), a few years later, confirmed Raab's work and showed, furthermore, that the potentiat-

ing effect of carbon dioxide and oxygen deficiency on the vasomotor center persisted after bilateral elimination of the carotid sinus. In their experiments they used from 3 to 4 per cent of carbon dioxide during the administration of the anoxia and observed a noticeable effect on the blood pressure. These workers believed that this potentiating effect on the vasomotor center by relatively small amounts of carbon dioxide was of benefit to the organism during anoxia.

The effect of rapid ascents to high altitudes upon the blood pressure in man.—A series of papers (27, 52, 54, 71, 76) dealing with the circulatory responses to oxygen deficiency, as experienced during the short exposures in aviation, was published under the direction of Dr. E. C. Schneider, from the Medical Research Laboratory of the Air Service of the Army. In the main, these reports showed that in a rapid ascent to 15,000 or even 20,000 feet, if the subjects were in good compensation and if the psychic factor was not active, the systolic blood pressure remained practically unchanged. Occasionally, however, a slight rise of 10–15 mm. Hg was found. The diastolic pressure, too, remained practically unaffected up to an altitude of 15,000 feet. If higher altitudes were attained, the diastolic pressure slowly decreased by about 10 or 15 mm. Hg. If, however, the compensation to the lowered partial pressure of oxygen was inadequate, the subject was apt to faint; this oncoming syncope could be predicted by the fall in the systolic and diastolic pressures. Schneider and Truesdell (76) have described in detail the various types of circulatory reaction.

Recently McFarland (55) has reported that in ascents made by train from sea-level to an altitude of 14,890 feet, only three of seven subjects showed a slight rise in systolic and diastolic basal blood pressure. In the standing position only two showed a slight rise. In rapid ascent by airplane to 15,000 feet there was but slight rise in systolic blood pressure in three of four subjects, with no change in the diastolic pressure. One individual, however, showed an increase of 27 mm. Hg in the systolic pressure but only a 10 mm. Hg increase in diastolic pressure.

These reports corroborate, for the main part, the observations made by Schneider and his co-workers previously mentioned, name-

ly, that up to altitudes of 15,000 feet there is but little, if any, important change in the blood pressure in the normal individual.

It has been suggested (94) that the small rise in blood pressure occasionally seen at high altitudes may be beneficial to the organism, since the blood is shunted from the splanchnic area and skin and is made available for those parts most in need of it.

CHRONIC EFFECTS OF ANOXIA ON ARTERIAL BLOOD PRESSURE

Practically all investigators are agreed that people in normal health who live at high altitudes up to 14,000 feet or even higher have no elevation of the blood pressure. Schneider and Hedblom (73) and Durig (18) have reviewed the early literature on this subject. Dr. Somervell (79), who has had a vast amount of experience in mountaineering at extreme altitudes, states that blood pressure seems to be unaffected by altitudes. This applies, of course, only to the subject who shows good compensation. It is generally agreed that during an attack of mountain sickness there may be an elevation in both systolic and diastolic pressures.

McFarland and Edwards recently (56) made observations on the blood pressure of airmen who made transpacific flights at a mean altitude of about 9,500 feet. The average age of the group was thirty-two years. They reported that there was a general tendency toward low blood pressure and that six of the eight men had systolic blood pressures below 110 mm. Hg. It was concluded that these airmen became acclimatized to the high altitude and maintained a high degree of mental and physical efficiency throughout the flight. These observations coincide well with those made on dwellers at high altitudes.

THE EFFECT OF CARBON DIOXIDE ON THE BLOOD PRESSURE (ASPHYXIA)

It is to the point to consider briefly the effect of carbon dioxide on the blood pressure, since during asphyxia there is an accumulation of carbon dioxide in the blood and in the tissues. Gellhorn and Lambert (24) have stressed the fact that carbon dioxide produces a rise in blood pressure by direct action on the vasomotor center and, to a

much lesser extent, on the carotid and aortic bodies. Carbon dioxide thus acts differently from oxygen want, since it has been seen that oxygen want acts directly on the carotid and aortic bodies. Gellhorn and Lambert point out that this demonstrates that there is a fundamental difference between anoxia and asphyxia. The asphyxial rise in blood pressure is thought to be reduced somewhat by pressure reflexes arising in the carotid sinus and cardio-aortic regions.

THE EFFECT OF ANOXIA ON VENOUS PRESSURE

Schneider and Sisco (74) in 1914 found that normal healthy young men had a normal venous pressure at 6,000 feet. On Pike's Peak (14,100 feet), however, a fall between 20 and 87 per cent occurred in the venous pressure; the fall occurred slowly, and in some of the subjects it was not manifested until they had been at a reduced pressure for a half-day or more.

Later work by Schneider and Truesdell (77) in 1924, again using man as a subject, but using the rebreather method to induce anoxia, reported a fall in venous pressure beginning at about 16 per cent oxygen, which corresponds to an altitude of about 7,000 feet. This fall became more pronounced between 12 and 10 per cent oxygen. They attributed the fall in venous pressure, in part at least, to a dilatation of the splanchnic blood vessels.

In the studies reported on Pike's Peak no cases were seen in which the fall of venous pressure interfered with adequate filling of the heart to decrease cardiac efficiency. Studies reported on cardiac output during moderate degrees of anoxia appear to corroborate these findings, namely, that if there is a fall in venous pressure produced by the anoxia it does not interfere with adequate cardiac filling.

Sands and De Graff (69), in their studies of the effect of progressive anoxia on the heart, observed the effect of anoxia on the venous pressure. They found that up to the crisis (which occurred at 9 per cent) there was a slight tendency for the effective venous pressure to decrease. When the crisis was reached, however, the effective venous pressure began to rise; this rise continued until it reached very high levels. It was observed that the elevation of effective venous pressure was the most definite criterion for the beginning of the crisis.

More experimental laboratory studies are needed on the effect of anoxia on the venous blood pressure. The studies reported by Sands and De Graff should be augmented by investigations on the effect of various degrees of anoxia on venous blood pressure on both man and animals over longer periods of time.

EFFECT OF ANOXIA ON CAPILLARY BLOOD PRESSURE

It has been shown by Lombard that the average capillary will disappear at a pressure between 35 and 45 mm. Hg; the most compressible ones will disappear at a pressure of 15–25; and the most resisting ones, at 60–70. It was found on Pike's Peak (14,100 feet) that the capillary pressure in some subjects was slightly lower than at an altitude of 6,000 feet, while in others no difference could be observed (1).

Liebesny (53) in 1922, making observations on capillaries, reported that when persons travel from a low altitude to places of considerable height certain alterations in the blood flow through the capillaries take place. Instead of the capillaries being homogenously filled and the blood streaming through them rapidly, as occurs at low levels, the flow becomes impeded; and the vessels, owing to the apparent agglutination or sedimentation, present a beaded appearance. In 1924 Schneider and Truesdell (77), working with human beings and using the rebreather method to induce anoxia, came to the conclusion that capillary blood pressure very often is not affected by anoxemia but that in cases of extreme anoxic anoxia the flow of blood through the capillaries is gradually retarded and the blood passes from a homogenous to a granular appearance, the red blood cells sometimes even showing a clumped appearance. Their observations during extreme anoxic conditions agree with those made by Liebesny.

Krogh (48) in his book on the capillaries mentions that he observed capillary dilatation during anoxia. Vanotti (90) in 1931 also reported that he observed definite dilatation in capillary loops in the skin at high altitudes.

The conclusion which may be drawn, then, from experimental evidence available is that anoxia does not cause a rise in capillary pressure.

HEMORRHAGES AT HIGH ALTITUDES

The impression is rather prevalent that even at moderately high altitudes bleeding from the nose, mouth, lungs, and the stomach often occurs. This is probably a popular fallacy; the number of people who suffer from hemorrhages under these conditions has been exaggerated greatly. Major Hingston (41), medical officer of the 1924 Mount Everest Expedition, reported that none of the members suffered from hemorrhages. If hemorrhages do occur at high altitudes, they cannot be explained as being due to increased capillary pressure or, for that matter, to increased arterial pressure.

EFFECT OF ANOXIA ON THE LYMPH

Relatively little work has been reported on the effect of anoxia on the composition or circulation of the lymph. Drinker and Field (16*) in their monograph mention the effects of asphyxia and carbon dioxide inhalation on lymph flow. They emphasize the importance of recognizing the fact that when lymph is collected from the thoracic duct any factor which causes an increase in breathing increases lymph flow. The augmentation in breathing produces an increase in intra-abdominal pressure during inspiration and suction of lymph into the thorax.

These authors point out that, since anoxia increases capillary permeability, it produces a condition which is presumably favorable to augmenting an increase in the flow of lymph. Although they recognize that increasing carbon dioxide produces dilatation of arterioles and capillaries, they are not confident that carbon dioxide actually increases lymph flow, since it greatly augments breathing. They subjected two dogs to 7 per cent carbon dioxide and observed an increase in the flow of lymph from vessels in the leg; but, since there was an increase in breathing, they suggested that the experiments should be repeated on curarized dogs and the breathing controlled artificially.

A pronounced stagnant anoxia may produce an increased filtration of lymph from the blood capillaries and so cause an edema. Drinker and Field (17) call attention to the fact that it is quite difficult to produce an edema by venous stasis. If a widespread venous thrombosis is produced, however, an edema is caused which is rich in protein. The authors interpret this to mean that, in order to produce edema in the presence of a normal arterial blood flow, the circulation must be obstructed sufficiently to produce asphyxial damage to the capillary endothelium. This means, of course, that a severe degree of anoxia must be produced before there is any appreciable effect.

* See p. 97 for bibliographical references.

Maurer (57) recently reported studies on the effect of decreased blood oxygen and increased blood carbon dioxide on the flow and composition of cervical and cardiac lymph. The experiments were done on dogs, which were subjected to anoxia by use of the rebreather. He found that increased lymph production began when the arterial oxygen saturation reached 75 per cent (approximate altitude of 17,000 feet) and that the greatest production took place at an arterial saturation of 52.5 per cent (approximately 20,000 feet altitude).

Since the increased flow of lymph persisted even after exposure to pure oxygen and since erythrocytes appeared in the lymph, Maurer felt that the anoxia damaged the cardiac blood capillaries. The increased passage of protein from the blood stream into the lymph indicated that low blood oxygen and increased carbon dioxide caused an increase in capillary permeability, so that there was a loss of fluid and protein from the circulating blood.

In a subsequent paper Maurer (58) reported the effects of carbon monoxide on the flow and composition of lymph. Dogs and cats under nembutal anesthesia were exposed to 0.5 per cent carbon monoxide. An average increase of flow of cervical lymph 2.42 times the control flow was observed. Since the increase in lymph production began when the average oxygen saturation was 61 per cent, the author pointed out that the results obtained with carbon monoxide compared favorably with those obtained when the animals were subjected to anoxic anoxia. He suggested further that this confirmed the belief that carbon monoxide is, of itself, nontoxic and that it acts only through its ability to reduce oxygen-carrying capacity. Some authors, however, would not concur with him in this belief and feel that he based his conclusions on insufficient evidence. The reader is referred to the discussion concerning the question of histotoxic action of carbon monoxide on page 13.

In summary, it may be said that there is good evidence that anoxia, produced either by allowing the animal to breathe air poor in oxygen (anoxic anoxia) or by allowing it to breathe air containing carbon monoxide (anemic anoxia), causes an increase in the production of lymph. An increased filtration of lymph may also be produced by pronounced degrees of stagnant anoxia. In view of the known

facts concerning the effect of anoxia and of carbon monoxide on the permeability of blood vessels, it is reasonable to suppose that the increase in the flow of lymph and the increase in its protein content produced by anoxia is due to increased permeability of the blood capillaries. Further studies are needed, however, on the effect of anoxia on both the flow and the composition of lymph.

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EFFECT OF ANOXIA ON RESPIRATION

The influence of anoxia on respiration has engaged the attention of investigators for many years, and a vast amount of data on this subject has been published. The reader is referred to the monographs of Barcroft (4*), Haldane (36), Haldane and Priestley (41), J. L. Henderson (49), Y. Henderson (52), Loewy (72), Loewy and Wittkower (74), Meakins and Davies (76), Means (77), Mosso (79), and Zuntz *et al.* (106) and to the reviews of Haldane (38) and of Schneider (88, 90).

Studies on low oxygen tension have taught us much about the method of control of respiration. The late J. S. Haldane especially deserves a great deal of credit for initiating studies upon which our interpretations today largely depend.

Jourdanet (66) in 1888, working in the mountainous districts of Mexico, is generally credited as being the first to report systematic observations of the effects of high altitude on respiration. Most of the early studies were made on the rate, depth, and per minute volume of breathing at high altitudes, since alterations in these could be readily observed and studied without elaborate or cumbersome apparatus. These early studies (21, 27, 79, 106) showed that the amount of change varied considerably with individuals.

THE CHANGES IN THE COMPOSITION OF THE ALVEOLAR AIR

One of the important effects produced by anoxia on the body is that it causes a fall of alveolar carbon dioxide tension. It is known that at low altitudes a close relationship exists between alveolar tension of carbon dioxide and the per minute volume of breathing; the two vary proportionally, and the carbon dioxide tension remains practically constant. The opposite is true at high altitudes. The augmented breathing produced by the anoxia washes out the carbon dioxide from the lungs, and, as a result, the carbon dioxide tension decreases with altitude. By noting the changes of carbon dioxide and oxygen in the alveolar air, it may be determined when and to

* See p. 124 for bibliographical references.

what degree the respiration responds to altitude. As early as 1906 Zuntz and his co-workers (106), by use of indirect methods, reported that the alveolar carbon dioxide tension was lowered as the barometric pressure fell. This was also reported by Durig (21) in 1909 on his Monte Rosa Expedition. Boycott and Haldane (12) early applied the direct method of studying this problem by placing subjects in a low-pressure chamber. They found that the alveolar carbon dioxide pressure was lowered and remained so for some time after the subjects were removed from the chamber. Ward (102) worked in con-

TABLE 8

THE EFFECT OF ALTITUDE ON THE ALVEOLAR CARBON DIOXIDE AND OXYGEN TENSION IN THE LUNG*

Place	Altitude (Feet)	Barometer (Mm. Hg)	Water Vapor (Mm. Hg)	Carbon Dioxide (Mm. Hg)	Oxygen (Mm. Hg)
Sea-level	0	760	47	42	100
Colorado Springs	6,000	620	47	36	79
Pike's Peak	14,000	460	47	28	53
North Col of Everest	21,000	335	47	19	39
Summit of Everest	29,000	240	47	15	24 (?)

* Modified from Y. Henderson, *Adventures in Respiration* (Baltimore: Williams & Wilkins Co., 1938), p. 79.

As the altitude increases, both the alveolar carbon dioxide and the oxygen alveolar tension fall. There is no change in the water-vapor pressure. Henderson has pointed out that the relations in the figures in the table essentially are:

(Barometric pressure − 47) × 0.2 = Carbon dioxide + Oxygen.

junction with the last-mentioned workers and, after a stay on Monte Rosa, found that the low alveolar carbon dioxide pressure persisted for some time after returning to sea-level.

Members of the Anglo-American Expedition (19) in 1911, upon their arrival on Pike's Peak (altitude 14,100 feet), found that the average alveolar carbon dioxide tension was 32.8 mm. Hg. It fell gradually during the next 19 days to between 25.4 and 29.5. The oxygen tension in the alveoli rose from 40.2 to 47.1 from the first day to finally 54.0–56.4. The decrease in alveolar carbon dioxide tension allowed the oxygen pressure to rise about 16 mm. above what it was upon their arrival. This increased oxygen content in blood, caused by the lowering of alveolar carbon dioxide pressure, is known as the "Bohr effect" and is due presumably to the action of carbon dioxide as an acid.

Miss Fitzgerald (25, 26) has shown from studies made on acclimated inhabitants at many altitudes that there is a rather constant relationship between barometric pressure and alveolar carbon dioxide pressure. She formulated a law that there was an approxi-

TABLE 9

SHOWING THE CHANGES IN THE ALVEOLAR AIR, VOLUME OF BREATHING, AND HEMOGLOBIN OF THE BLOOD DURING ACCLIMATIZATION TO ALTITUDE AND AFTER RETURN TO SEA-LEVEL*

Altitude (Feet)	Days after Arrival	Alveolar Carbon Dioxide (Mm. Hg)	Volume of Breathing (Percentage of Sea-Level Volume)	Hemoglobin (Percentage of Normal)
Sea-level	100+	40	100	100
6,000	1	37	108	100
	2	36	111	100
	3	35	115	101
14,000	1	32	125	103
	2	31	129	106
	3	30	133	108
	5	29	138	109
	10	28	143	113
	20	27	148	116
	35	26	154	120
6,000	1	29	138	112
	2	31	129	110
	3	33	121	108
Sea-level	1	36	111	105
	2	39	102	104
	5	40	100	102
	30	40	100	100

*From Y. Henderson, *Adventures in Respiration* (Baltimore: Williams & Wilkins Co., 1938), p. 89.

mate fall of 4.2 mm. alveolar carbon dioxide pressure for every fall of 100 mm. Hg in barometric pressure. Schneider (90) has pointed out that this means that, in acclimatization, for each 5,000 feet of rise in altitude approximately a 15 per cent increase in the ventilation of the lungs occurs. Somervell (98), during the 1922 Mount Everest Expedition, made alveolar air analyses at 16,500 feet and at 23,000 feet and found the alveolar oxygen tension somewhat higher and the carbon dioxide tension somewhat lower than would be expected by

applying Fitzgerald's law. His results, however, have been criticized, since he collected the air samples in a rubber bag and since it is known that carbon dioxide may diffuse through a rubber membrane.

Schneider and his co-workers (93, 75) have made studies on alveolar carbon dioxide and oxygen tensions in a low-pressure chamber

TABLE 10

STUDIES ON MAN IN A LOW-PRESSURE CHAMBER*

	BAROMETRIC MEASURE (MM. HG)					
	760	656	560	480	410	352
Altitude in feet	0	4,000	8,000	12,000	16,000	20,000
Oxygen pressure in mm. Hg	103.2	83.7	66.0	53.3	42.6	34.8
Carbon dioxide pressure in mm. Hg	39.7	37	36.2	33.6	31.3	30.0

* From Lutz and Schneider, *American Journal of Physiology*, 50, 280, 1919.

TABLE 11

STUDIES ON MAN DURING AIRPLANE FLIGHT*

	ALTITUDE (FEET)				
	0	4,000	8,000	12,000	15,000
Oxygen pressure in mm. Hg	100.5	90.5	67.2	58.1	49.8
Carbon dioxide pressure in mm. Hg	40.9	35.3	35.7	32.5	29.2

* From Schneider and Clark, *American Journal of Physiology*, 76, 354, 1926.

and during actual airplane flights. Tables 10 and 11 give their results. The results they obtained by both methods were quite comparable. Both sets of data show that an increase in pulmonary ventilation occurs before an altitude of 4,000 feet is reached. Haldane and Poulton (40) have pointed out, however, that the barometric pressure must be reduced about one-third before there is any effect on breathing. The increased pulmonary ventilation washes out the carbon dioxide from the lungs and from the blood, so that the arterial carbon dioxide tension falls. This is obviously undesirable, since the

carbon dioxide is needed to stimulate the respiratory center. In spite of the lack of this stimulus, however, it has been found that the augmentation of respiration continues at high altitudes. There is considerable proof that the oxygen lack per se is capable of indirectly stimulating the respiratory center (regarding respiration center see p. 107). The lowering of the arterial carbon dioxide pressure also produces certain changes in the chemistry of the blood, which have been discussed (see p. 59).

THE AQUEOUS VAPOR PRESSURE IN THE LUNGS

In a discussion involving the changes in the composition of the alveolar air brought about by anoxic anoxia the aqueous pressure in the lungs must be considered. It is generally stated that a pressure of 47 mm. Hg (corresponding to an altitude of 62,965 feet) is the minimal pressure at which the alveoli of the lungs are able to absorb gases, since this pressure is that which the water vapor exerts in the lungs. If at the altitude of 62,965 feet the body fluids were brought into contact with the atmosphere, they would boil.

Armstrong (2) has pointed out, however, that this figure is incorrect and that the alveolar oxygen partial pressure in the lungs reaches zero at 86 mm. Hg (50,313 feet). He accepts the fact that 47 mm. Hg is usually given as the water vapor pressure in the lungs, but he points out that the alveolar carbon dioxide also exerts a pressure of 39 mm. Hg and that this figure must be added to that of the water vapor pressure (47 mm. Hg); this would make a total of 86 mm. Hg. Armstrong maintains that this important factor has been overlooked by most workers. In this connection it must be mentioned, however, that the hyperpnea produced by the anoxic anoxia would tend to reduce the alveolar carbon dioxide tension, as Tables 10 and 11 show. The tension of the water vapor in the lungs, of course, does not change (see Table 8).

THE RATE OF RESPIRATION

In the unacclimatized subject, if he is at rest and the rate of ascent is not too rapid, an increase in respiration develops only gradually, so that he may not be aware of the change. Schneider and his co-workers (75) found, with experiments performed in a low-pressure chamber, that the rate of respiration was not affected par-

ticularly until a simulated altitude of 15,000 feet was reached. Hingston (59) stated that even at great altitudes, if the body remained at rest, the rate of breathing was apparently normal and as comfortable as at sea-level. Other writers, however, have reported that changes may manifest themselves as low as 4,000 feet (3, 23). J. S. Haldane and Poulton (40) found a considerable individual variation, since some people will show an increase in breathing if the oxygen per cent is lowered 5 per cent, but in most individuals a lowering of 7 per cent is needed. In a few individuals no effect is observed in breathing until consciousness is lost; it obviously is dangerous for these persons to ascend to high altitudes.

If the subject engages in severe exercise, however, the rate becomes greatly increased (ten to fifteen times) even at moderate altitudes (p. 110). If the respiration is stimulated enough to wash out the carbon dioxide from the lungs and from the arterial blood, so that an alkalemia develops, the respiration will be somewhat decreased, as previously stated.

It is well known not only that the frequency of respiration may develop slowly during the reduction of the barometric pressure but that the depth of respiration, too, may develop so gradually that the subject is not conscious of the change. An airplane pilot, then, often cannot determine when it is necessary to begin to take oxygen, since there may be no feeling of breathlessness or noticeable increase in the frequency or in the depth of respiration. Men may lose consciousness without experiencing any feeling of breathlessness at all. This is, indeed, an important observation.

THE DEPTH OF RESPIRATION

It is thought that the depth of respiration is increased more by anoxia than is the rate. Lutz and Schneider (75), from experiments made in a low-pressure chamber, reported that in some men an increase in pulmonary ventilation began at pressures comparable to altitudes of 3,000 and 4,000 feet; over 50 per cent of the men, however, showed no increase until altitudes from 7,000 to 10,500 feet were simulated, and they found an occasional man who did not respond at all. The effect of anoxia, then, on the depth of respiration also varies greatly in different individuals.

THE PER MINUTE VOLUME OF BREATHING

The increase of the depth in breathing at high altitudes, which has just been mentioned, is largely responsible for the increase in the per minute volume of breathing. With a fall in alveolar carbon dioxide tension there is a concomitant increase in the per minute volume of breathing, and Lutz and Schneider (75) have shown that breathing is, indeed, delicately responsive to rapid changes in altitude. In a series of experiments performed in a low-pressure chamber they demonstrated that pulmonary ventilation in a sensitive person varies directly with the altitude. Their experiments suggested that there was a linear relationship between the per minute volume of breathing and altitude. It is thought (90) that in acclimatization for about every 5,000 feet increase in altitude a 15 per cent increase in ventilation of the lungs occurs. It seems, however, that the increase in the per minute volume of breathing at high altitudes is more apparent than real. Schneider (90) has shown that, if the volume of air breathed at an altitude of 15,000 feet is corrected for temperature and pressure by reducing the volume to 0° C. and 760 mm. Hg, the total volume breathed is from 10 to 78 per cent less than at low altitudes.

THE EFFECT OF ANOXIA ON THE RESPIRATORY CENTER

It is known that, initially, oxygen lack stimulates respiration. Haldane and Priestley (42) in 1905 stated that the oxygen of respired air must fall to 13 per cent of an atmosphere before the respiratory center is stimulated. In 1919 Ellis (23) reported, however, that for normal men respiratory stimulation may occur when there is a decrease to 18 per cent oxygen in the inspired air. As Schmidt and Comroe (87) have pointed out, this is probably the highest acceptable value. It was shown by Gasser and Loevenhart (28) in 1914 that injections of threshold doses of sodium cyanide or carbon dioxide affected the respiratory center before any other body function was measurably influenced. They felt that this indicated that the cells of the respiratory center were more sensitive to decreased oxygen fixation than any other cells in the body. These workers, of course, made their observations before the discovery of the function of the carotid sinus.

The exact stimulus of the respiratory center produced by anoxia is not entirely understood. This is not unexpected, since there still is a good deal of controversy regarding the nature of the stimulus to the respiratory center in an animal under normal barometric pressure.

It was held by Hasselbalch and Lindhard (46) in 1911 that the respiratory center became more sensitive to carbon dioxide as the oxygen tension decreased. On the other hand, Campbell *et al.* (14) in 1913 maintained that the alveolar oxygen tension could be varied within wide limits without sensibly affecting the respiratory response to carbon dioxide, and recent work (22, 96) appears to indicate that the respiratory response to carbon dioxide is decreased during anoxia. Y. Henderson (53) holds that the excitability of the respiratory center is largely determined by the tension of oxygen in the blood.

Chemoreceptor reflexes.—A mass of evidence has been produced within the past few years to show that, in the intact animal, anoxia stimulates the respiratory center reflexly by acting on the sensory nerve endings in the aortic arch and carotid bodies. It is thought that the reflexes from these structures are largely, if not entirely, responsible for the stimulant effects of anoxia on respiration. The extensive literature in this field recently has been reviewed from several viewpoints (30, 57, 86, 87). The reader is referred to these reviews for important details concerning this interesting subject.

Schmidt and Comroe (86, 87) have stated that in their judgment the available evidence indicates that the threshold of the chemoreceptors to anoxemia is decidedly less than that of the respiratory center. Furthermore, they have pointed out that the balance of experimental evidence indicates that the chemoreceptors are less sensitive to carbon dioxide than the respiratory center. They postulated that under certain conditions (such as anesthesia) the control of breathing may be carried out by the chemoreceptors, which are responding to deficiency in the oxygen tension of arterial blood rather than to increase in carbon dioxide tension, and that, under these conditions, sudden relief of anoxemia may cause respiratory failure.

On the isolated center anoxia is thought to have a depressant action, for, if the vagi and the nerves from the carotid sinus are sev-

ered, oxygen lack will produce a respiratory paralysis (15, 24, 29, 31, 32, 58, 85, 96, 97, 104, 105).

Finally, it is thought that the sensitivity of the respiratory center (and perhaps the chemoreceptors) of an individual is of considerable importance in successful adaptation to very high altitudes. It is known that presumably normal individuals show a marked variation in the sensitivity of the respiratory center to anoxia; if the center fails to respond at great heights, death may, of course, ensue.

Haldane (36) has stressed the fact that anoxia fatigues the respiratory center, which is manifested by diminished depth in breathing. Owing to this fatigue produced by anoxia, the respiratory center almost always stops before the heart does. When failure of the center seems imminent, artificial respiration will compensate for the fatigued condition; it may be necessary, however, to maintain artificial respiration for a long time. Haldane, furthermore, has pointed out that a diminished depth of breathing with increasing rate is a sign of onset of fatigue of the center. If, on the other hand, there is a diminished depth with no increase in rate, the subject is in immediate danger of death. As a rule, death from anoxia at high altitudes is due to the failure of the respiratory center. Haldane has also stated that, once the respiratory center is fatigued, the effects may persist for a long time, so that individuals may subsequently suffer from shallow breathing during exercise or rest. This was observed in cases of neurasthenia during the last World War.

EFFECT OF MUSCULAR ACTIVITY ON RESPIRATION

While it is generally believed that the slightest exertion at high altitudes brings on dyspnea, experiments performed by Schneider and Clark (94) have shown that this is true only in part. Investigations made on a bicycle ergometer in a low-pressure chamber showed that with a load of work of 2,000 foot-pounds the per minute ventilation of the lungs at simulated altitudes of 10,000 feet was 10 per cent larger than at sea-level; at 15,000 feet it was 11.4 per cent larger than at 10,000; at 20,000 feet, 14.7 per cent larger than at 15,000 and at 25,000 feet, 25.6 per cent larger than at 20,000.

That extremely high altitudes are quite capable of producing hyperpnea is well known. Hingston (60), reporting the physiological

difficulties in climbing Mount Everest, wrote: "But the very slightest exertion, such as the tying of a bootlace, the opening of a ration box, the getting into a sleeping bag, was associated with marked respiratory distress." He also gives Somervell's experience: "Somervell gives a record of his breathing at 27,000 feet. At that altitude he had to take 7, 8 or 10 complete respirations for every single step forward and even at that slow rate of progress he had to rest for a minute or two every 20–30 yards. At 28,000 feet Norton, in an hour's climb, ascended only about 80 feet."

Schneider (90) has pointed out that, while at sea-level a rectilinear relationship during physical exertion ordinarily is maintained

TABLE 12

THE EFFECT OF ALTITUDE ON RESPIRATORY RATE*

	Sea-Level	Pike's Peak (14,100 Feet)
In bed	16.8	17.3
Standing	17.0	20.0
Walking: 4 miles per hour	17.2	29.0
Walking: 5 miles per hour	20.0	36.0

* From Schneider, *Yale Journal of Biology and Medicine*, 4, 537, 1932.

between the per minute volume of breathing and the load of work up to the crest load, investigations in the low-pressure chamber showed that, with moderate reduction of barometric pressure, pulmonary ventilation maintained the linear relationship with the load. It broke down, however, at atmospheric pressures comparable to altitudes above 15,000 feet with heavy loads.

The Anglo-American Pike's Peak Expedition reported that the volume of air breathed in an acclimatized subject at 14,100 feet while walking at the rate of 4.5 miles per hour was 50 per cent greater than while walking at the same rate at sea-level, and 100 per cent greater while undergoing severe muscular exercise similar to that performed at sea-level. As Schneider has pointed out, a 32–50 per cent increase in pulmonary ventilation during rest is not subjectively noticeable; but if the volume of breathing is large at sea-level for a given load, then 50–100 per cent increase at high altitude becomes

excessive. Hyperpnea is certainly much more likely to occur at high altitudes than at sea-level.

As already mentioned, the breathing at high altitudes during rest is ordinarily increased only in depth. The frequency of breathing, however, during exercise increases more rapidly than at sea-level. This is not unexpected, since this is the simplest method of augmenting the pulmonary ventilation. Table 12 shows the increase in respiration produced by high altitudes at rest and during exercise.

To the figures given in Table 12 might be added the observations of Somervell (98), who, while climbing Mount Everest at an altitude of 28,000 feet, reported that his respiratory rate was between 50 and 65 per minute.

THE ABILITY TO HOLD THE BREATH

The ability to hold the breath at high altitudes is not decreased until acclimatization occurs. Schneider (88) performed the following interesting experiment on himself. In a low-pressure chamber at simulated altitudes of 10,000, 14,000, and 16,000 feet he was capable of holding his breath for 122, 128, and 120 seconds, respectively. Normally, at sea-level he was able to hold his breath for 120 seconds. The breaking-point, then, was not determined by the oxygen want. It is proved that at sea-level it is practically impossible voluntarily to hold one's breath until unconsciousness supervenes. At simulated altitudes of 14,000 and 16,000 feet, however, Schneider held his breath until he became unconscious. Unlike holding his breath at sea-level, his co-workers observed that he showed a pronounced degree of cyanosis.

After acclimatization to a high altitude the breath-holding ability is greatly reduced. Hingston (59) reported that on one of the Mount Everest expeditions at an altitude of 21,000 feet he could hold his breath for only 14 seconds, while at sea-level he could hold it for 64 seconds. Schneider (89), as previously mentioned, could hold his breath at sea-level for 120 seconds; but when he lived at Colorado Springs (altitude, 6,000 feet), he could hold it only from 60 to 73 seconds. On the second day of one of his expeditions to Pike's Peak (14,100 feet) he held his breath for 62 seconds; on the third day, 54 seconds; the fourth day, 49 seconds; the fifth day, 43 seconds; the sixth day, 38 seconds; the eighth day 43 seconds; and the ninth day,

34 seconds. His breath-holding ability, then, showed a marked reduction as acclimatization was taking place.

The reason for this decrease in the breath-holding ability is not entirely clear, but it is most likely associated with the decrease in the alkaline reserve of the blood. It is known that the alveolar carbon dioxide tension falls during the period of acclimatization.

AFTEREFFECTS ON RESPIRATION AFTER EXPOSURE TO HIGH ALTITUDE

The aftereffects on respiration after exposure to high altitude depend upon the length of time of the exposure.

Short exposure.—It was reported by Lutz and Schneider (75) that in four of five men who had been subjected to a barometric pressure equivalent to 15,000 feet in a low-pressure chamber for 30–90 minutes the alveolar carbon dioxide tension was back to normal within 20 minutes after returning to normal atmospheric pressure. Boycott and Haldane (12) found that in a subject who had been kept in a low-pressure chamber at 545 mm. Hg (equivalent to an altitude of about 9,000 feet) for 24 hours the alveolar carbon dioxide pressure had not returned to normal at the end of 2 days.

The aviator breathes subnormally for a while after he descends; during this time the body is recovering from the loss of carbon dioxide, and bicarbonate is being reformed in the blood.

Long exposure.—Several authors have reported (19, 91) on the persistence of aftereffects following long sojourns at high altitudes. According to Apperly (1), at the moderate altitude of 6,000 feet there is little or no hyperventilation during the first day or two, and the alveolar carbon dioxide remains practically unchanged. Within a few days, however, there is an increasing hyperventilation with a fall of alveolar carbon dioxide and loss of blood alkali. After a return to sea-level the hyperventilation continues, as does the loss of blood alkali. He interprets this to mean that the primary change is an increased sensitivity of the respiratory center and believes that recovery from this change is a slow process.

Schneider (91) reported the interesting case of a man who had lived on the summit of Pike's Peak (14,100 feet) for six months. After his return to Colorado Springs (6,000 feet) he continued to

show a hyperpnea for approximately 4 weeks, during which time the alveolar carbon dioxide tension rose from 27.1 to 37 mm. Hg.

The mountaineer, therefore, ventilates his lungs excessively upon his return to the lowlands, in contrast to the aviator, who breathes subnormally when returning from a flight. The difference may be explained on the basis of the chemistry of the blood. The aviator has an alkalosis of the blood; the blood of the mountaineer has approximately a normal hydrogen-ion concentration but a reduced alkaline reserve. He will continue to ventilate his lungs excessively until the alkaline reserve of the blood is normal for the altitude in which he lives.

PERIODIC BREATHING

Unacclimatized subjects at high altitudes often show a change in their breathing pattern. This was first described by Mosso (79). Respiration becomes irregular and resembles the Cheynes-Stokes type of breathing, although it differs from it in some respects. This irregularity most frequently occurs during sleep at night. It is caused by oxygen want, as shown by the fact that the administration of oxygen abolishes it. The breathing pattern shows much individual variation, but ordinarily the breaths occur in groups of three or four, each successive breath being deeper; and an apneic pause may follow the last one. Aviators flying at high altitudes may be troubled by this periodic breathing, and Birley (10) reported a case in which it became so marked that the pilot had difficulty in controlling the airplane. Hingston (59) observed this in members of the Mount Everest Expedition and wrote: "I heard one member of the party breathing in this way as low as 12,000 feet, though as a rule, it seldom occurs when awake, yet at the base camp I was conscious of this type of breathing before passing off to sleep. Illness at high altitudes markedly increased it."

When acclimatization becomes established, the tendency to periodic breathing disappears. Schneider (88) emphasizes the point that the onset of periodic breathing ordinarily is brought about by a pause in breathing, and he calls attention to the experiences of the members of the Anglo-American Expedition to Pike's Peak. The first few days, when they read gas burettes or shaved or performed any task which called for close attention, periodic breathing would manifest

itself, since in tasks of this nature most people unconsciously hold their breath.

The pronounced individual variation in susceptibles to periodic breathing was attributed by the Anglo-American Expedition to varying susceptibilities of the respiratory center. If the individual had a respiratory center responsive to anoxia, he suffered from frequent attacks of periodic breathing, while the reverse was the case in a man whose breathing responded slowly to the change in altitude.

SIZE AND SHAPE OF CHEST AT HIGH ALTITUDES

It has been reported by a number of observers that inhabitants of high altitudes have enlarged chests. It is generally conceded that this is true only for those who have grown up at high altitudes, although reports (48, 103) have been made in the literature that chest enlargement may occur after a prolonged sojourn at high altitudes. Rengger-Perlmann (83) reported that the male adults at Davos (5,200 feet) had an increased circumference of their chests. Loewy and Marton (73) found also that the children at Davos showed an increase in chest circumference. Hurtado (61) measured the chest circumference of inhabitants between the ages of four and seventy-five at Morococha (16,300 feet) and showed that from childhood on the chest was unusually developed. Barcroft *et al.* (5) showed, by means of the x-ray, that in the Cholos living in the high Peruvian Andes the direction of the ribs was more horizontal than in lowlanders. The average value of the slope of the ribs in the members of Barcroft's party was 21°, while the average of the Cholos was only 13. Barcroft mentioned that the chests of Peruvian laborers at an altitude of 14,200 feet were unusually broad and deep, and he wrote as follows: "Without laying too much stress on the shape, the above information may be summed up roughly by saying the native of five feet three inches has the chest of a man six feet" (5).

CHEST EXPANSION

Chest expansion is increased in inhabitants at high altitudes. It was observed by Loewy and Marton (73) in children at Davos, and in male adults in the same locality by Rengger-Perlmann (83), that the chest expansion was greater than in those who lived at lower levels. Hurtado (61) obtained similar findings in Peruvian natives. He re-

ported that the average difference between full inspiration and expiration in young adolescents was 3.5 inches; in adults, 3.2 inches; and in old people, 2.9 inches. By way of comparison, he considered the average chest expansion of a North American student, who was much taller and better developed physically than the natives as 2.9 inches.

THE EFFECT OF ANOXIA ON VITAL CAPACITY

It has been shown by a number of workers that a lowered barometric pressure produces a decrease in vital capacity. It was first noticed by Paul Bert in 1878 (9). A number of explanations have been offered as to the cause of this. Some of the older views will be given here because of their ingenuity. Zuntz and his co-workers (106) in 1906 thought that the decrease was due to the expansion of intestinal gases; Durig (21) in 1909 suggested it was due to the fatigue of the respiratory muscles; Fuchs and Deimler (27) in the same year described it as being due to increased muscle tone caused by the low temperature. In a later paper Durig and Zuntz partly accepted the latter view.

Schneider (92), by experiments performed in a low-pressure chamber, found that a decrease in vital capacity did not ordinarily occur at simulated altitudes of less than 10,000 feet. In the majority of cases, the change occurred at simulated altitudes from 12,000 to 15,000 feet. A good deal of individual variation was noted. At a simulated altitude of 20,000 feet there was an average decrease in vital capacity of 350 cc., or approximately 8 per cent. It was found that if oxygen were administered to these subjects it tended to restore the vital capacity to normal. Experiments were carried out also on Pike's Peak (14,100 feet). In nine men the vital capacity was decreased during the first day or two from 6.7 to 15.3 per cent. After acclimatization occurred, the vital capacity returned to normal. Grollman (34) in 1930 also made some observations on vital capacity on Pike's Peak. He found that his own vital capacity was decreased 11.2 per cent.

In 1922 Drinker, Peabody, and Blumgart (20) reported work which suggested that an engorgement of the pulmonary blood vessels probably takes up alveolar space and in this way decreases vital capacity. Bartlett (8) in 1903 had presented evidence which showed

that diminished air pressure caused the pulmonary vessels to dilate, thereby producing a congestion in the lesser circulation. He attributed this to an equalization of the atmospheric and intrathoracic pressure. In point of fact, a number of investigators (13, 65, 71, 84, 99, 101) have reported that anoxic anoxia may produce congestion and dilatation of the lung capillaries. Schubert (95) in 1930 postulated that in rarefied air the alveolar walls relax and that their lumen becomes smaller because the elastic force of the alveoli has less to oppose. Other workers (13, 48, 61, 62, 67, 82), however, have described an emphysematous appearance of the lungs and a dilatation of the alveolar spaces.

Schneider (92), from his own work, suggested that the reduction in vital capacity at high altitudes was due to an engorgement of pulmonary vessels, that reserve capillaries opened up, and that anoxia possibly produced a relaxation of pulmonary capillaries. He felt that the administration of oxygen restored the tone of these capillaries and, in this way, restored the vital capacity to normal. Schneider's view is shared by Monge *et al.* (78) and by Hurtado and Guzman-Barron (63).

VITAL CAPACITY OF INHABITANTS AT HIGH ALTITUDES

The decrease in vital capacity noticed in unacclimatized subjects is only temporary, and most authors feel that there is an actual increase in vital capacity after acclimatization has taken place. It must be mentioned here, however, that Izquierdo (64) reported that the vital capacity of two hundred inhabitants at an altitude of 7,450 feet did not vary from the normal ranges, and Ocaranza (81) found no increase in vital capacity of men acclimatized to the valley of Mexico. Rengger-Perlmann (83), however, found an increase in the average vital capacity in thirty males at Davos (5,120 feet). An average of 4.7 liters was reported, whereas, according to their height, normally the figure should have been 3.7 liters at sea-level. Loewy and Marton (73) also found an increase in vital capacity of children at Davos.

Hurtado (54), working with Peruvian children, also concluded that the vital capacity was raised above the normal. He reported, further, that the vital capacity of the mountainous inhabitants di-

minished with increasing age, as it does with those who live at sea-level.

It must be remembered that high altitudes alone do not cause an increase in vital capacity, but physical training also increases it. An interesting study of the athletes at the Olympic Winter Games at Saint-Moritz showed that the physically trained lowlanders had about the same vital capacity as the Swiss highlanders (72).

THE QUESTION OF OXYGEN SECRETION BY THE LUNGS AT HIGH ALTITUDES

It is now generally accepted that, normally, the membrane of the lung between the blood and the alveolar air plays only a passive role and that oxygen passes into the blood by simple diffusion. Bohr (11) in 1890 held the view, and others had before him (Ludwig), that the pulmonary epithelium actively secreted oxygen. In point of fact, there have been two schools of thought on this question, and the controversy regarding this issue is still alive. The late J. S. Haldane was the chief champion for the view that the lung epithelium secreted oxygen at high altitudes, and the reader is referred to his writings (36, 38, 41).

In 1912 Haldane expressed the view that if oxygen pressure is low in the alveoli, the pulmonary epithelium may secrete oxygen in order to bring about a higher tension in the arterial blood than in the alveolar air. He further claimed this could be demonstrated at high altitudes by allowing the subject to breathe a low percentage of carbon monoxide; if this were done, the blood in the body would be found to contain less carbon monoxide than would blood which had been shaken with the same alveolar air in vitro. The interpretation was that the lungs favored the uptake of oxygen and impeded that of carbon monoxide. Hartridge (43), however, could not confirm Haldane's findings.

The secretion theory of oxygen received considerable support from observations made by the Anglo-American Pike's Peak Expedition. Douglas, Haldane, Henderson, and Schneider (19), using methods of Haldane and his co-workers, reported that, according to their computations, the oxygen pressure in the arterial blood, which was found to be 88.3 mm. Hg, was 35.8 mm. higher than the normal

resting alveolar oxygen pressure of 52.5. Dr. Marie Krogh (70), in 1915, however, made the work of these authors untenable by establishing a new diffusion coefficient for the passage of oxygen through a membrane. She showed that at rest, even in an unacclimatized body, diffusion may take care of the oxygen requirement to an altitude of 25,000 feet (barometric pressure of 290 mm. Hg), which is about as high as is compatible with life in an unacclimatized individual.

In 1920 Barcroft *et al.* (7) reinvestigated the tensions of oxygen in the blood under anoxic conditions. By making an arterial puncture blood was drawn directly from the radial artery of a man who had been kept at an oxygen pressure of 84 mm. Hg (altitude approximately 17,000 feet) for 6 days. The oxygen pressure of the blood was carefully measured by the most approved methods. The conclusion was reached that during both rest and work less oxygen was contained in arterial blood in vivo than in samples of the same blood exposed to alveolar air in vitro at body temperature.

The experiments performed by members of the expedition to the Peruvian Andes in the winter of 1921–22 at a height of 14,200 feet also showed that the arterial oxygen tension was somewhat lower than the alveolar. Experiments performed on dogs by the Greenes (33) also supported this view.

Work done in the Colorado mountains by Dill *et al.* (18) in 1929 failed to support the secretion hypothesis, as did those experiments performed by Dill, Christensen, and Edwards (17) at very high altitudes in Chile in 1935. These workers all felt that the evidence fully confirmed Barcroft's conclusion that even at high altitudes oxygen passed into the blood by diffusion only.

The evidence appears to be overwhelming, then, that the lung membrane plays only a passive part and that the oxygen passes into the blood by physical diffusion even at high altitudes. It is of interest, however, that the late J. S. Haldane, in his recent work *Respiration*, published in 1935, steadfastly maintains that the lungs actively secrete oxygen in conditions of oxygen want.

THE CHEMISTRY OF RESPIRATION AT HIGH ALTITUDES

The effect of anoxia on the acid-base balance of the blood has been discussed (p. 59). It is known that respiration at high altitudes is

closely associated with changes which occur in the reaction of the blood. The relationship is a complex and far-reaching one, for it presumably embraces the factors responsible for the causation of mountain sickness and the explanation of acclimatization. There are many factors involved which, at present, are not understood; for example, no entirely adequate explanation has been given, as yet, for the cause of mountain sickness, nor are all the facts known concerning acclimatization. The reader is referred to the chapters dealing with these last two topics.

The acid-base balance of the blood is important, since changes in this balance affect the respiratory center and also the dissociation of oxyhemoglobin. Physiologically, it is known that an increase in the partial pressure of carbon dioxide stimulates respiration; it also augments dissociation of oxyhemoglobin (Fig. 2, p. 9). A decrease in the partial pressure of carbon dioxide has the opposite effect.

1. *Dissociation-curve studies.*—It was observed by the members of the Anglo-American Pike's Peak Expedition (19) that in acclimatized individuals, if the blood is exposed to a carbon dioxide pressure characteristic for the alveolar pressure of the altitude, the affinity of the hemoglobin for oxygen is the same as at sea-level. It has been shown that if blood from an acclimatized individual be exposed to 40 mm. Hg of carbon dioxide, which is the average alveolar tension at sea-level, the dissociation curve is shifted to the right, which indicates that there is an increase in acid radicals or a decrease in the bases of the blood (90). In order to explain these facts, a theory was suggested by Douglas *et al.* (19) that certain abnormal quantities of metabolites in the blood, produced by the anoxia, changed the threshold of alkalinity for the kidneys so that the alkalinity of the blood would be reduced and the acid-base relationship restored characteristic to that of acclimated persons.

In 1919 Haggard and Henderson (35) and in 1920 Y. Henderson alone (50) employed the carbon dioxide dissociation curve of the blood to show the amount of alkali in use in the blood. They reported that in anoxia augmented breathing began before a reduction of blood alkali occurred and that there was no lowering of the blood alkali before or coincident with the increase in breathing. They outlined the hemato-respiratory chain of events during acclimatization

as follows: (1) oxygen tension of inspired air lowered; (2) stimulation of respiratory center (decreased production of "respiratory *X*"); (3) excessive respiration which blows off the carbon dioxide; (4) a decrease in the carbonic acid/sodium bicarbonate ratio, indicating an alkalosis rather than an acidosis, as suggested by earlier writers; and (5) disappearance of alkali from blood by some compensatory mechanism.

When a reduction of blood alkali is produced by anoxic anoxia, Henderson (54) has suggested that the condition be called *acarbia*, which designates a subnormal bicarbonate rather than a condition of acidosis. This term is deserving of wider recognition and usage.

2. *Loss of carbon dioxide from the blood caused by low oxygen tension.* —The fall of alveolar carbon dioxide tension produced by anoxia has been discussed (p. 101). It is assumed theoretically that the alveolar carbon dioxide tension is proportional to the carbon dioxide tension in arterial blood. Paul Bert (9) as early as 1878, Mosso and Morro (80) in 1903, making direct measurements of the carbon dioxide content on dogs, and Sundstroem (100), taking measurements on himself, all found that low oxygen tensions cause a loss of carbon dioxide from the blood.

Y. Henderson (51) and later Henderson and Haggard (56) showed that when dogs were subjected to anoxia there occurred: (1) dyspnea, (2) a lowering of the carbon dioxide content of the blood, (3) increased hydroxyl ion concentration, and (4) the secretion of alkali by the kidney in order to restore the blood reaction. In 1919 Kellas, Kennaway, and Haldane (68) found that when man was subjected to oxygen want the secretion of urine also became alkaline, as it did in the dog experiments of Henderson. Lutz and Schneider (75) found that in men subjected to oxygen want for 60–90 minutes, even though the carbon dioxide was reduced and the normal ratio of carbonic acid/sodium bicarbonate was changed in the direction of a temporary alkalosis, the blood alkali was not reduced. During the first two days of a sojourn at 14,100 feet Sundstroem (100) found that, while the hydrogen-ion concentration of the blood indicated an alkalosis, the urinary secretion of base was less than it was later.

It was believed by Boycott and Haldane (12) that the hyperpnea produced by anoxia was due to accumulation of lactic acid formation

in the blood and that this increased lactic acid had the same effect on the respiratory center as did carbon dioxide, in that it sensitized the center to carbon dioxide, so that less was required to excite it. It has been shown, however, by several workers that lactic acid does not accumulate at high altitudes (p. 63). The theory postulated by Boycott and Haldane, then, is not tenable in the light of known facts.

3. *The effect of anoxic anoxia on the transport of carbon dioxide.*—It is of interest to consider briefly whether or not anoxic anoxia influences the transport of carbon dioxide. Under normal conditions 80 per cent of the transport of carbon dioxide is due to the base made available when oxyhemoglobin is reduced. It is conceivable that there could be serious interference with carbon dioxide transport if the anoxia became so severe that the hemoglobin of the arterial blood was already so reduced that this release of base could not occur. This likely would not happen much below 22,000–25,000 feet. Hastings (47) has stated that, for all practical purposes, carbon dioxide transport is probably not impaired until the circulation fails.

4. *Carbonic anhydrase activity during anoxic anoxia.*—It is in order, at this point, to take up briefly what effect, if any, anoxic anoxia may have on the activity of carbonic anhydrase, the enzyme which catalyzes the reaction $H_2CO_3 = CO_2 + H_2O$ and which appears to be so essential in respiration.

It will be recalled that the measurements of carbonic anhydrase activity are made in an atmosphere of carbon dioxide in the absence of oxygen and, further, that strong oxidizing agents inhibit its activity. In view of this, it would not be expected that anoxia would affect the activity of carbonic anhydrase, except in so far as the pH was influenced. Kiese and Hastings (69) investigated the activity of this enzyme in relation to the hydrogen-ion concentration over a range from pH 6.1 to 10.1. At a pH of 7.05 the concentration of enzyme preparation required to double the rate of hydration was 7.0 (expressed in gamma per 100 c.c); at a pH of 7.54 it required 3.7; and at a pH of 7.60 a concentration of 4.0 was required. These results would tend to show that the relatively slight increase in alkalinity, produced by the hyperpnea brought about by anoxia, probably

would not have a marked effect on the activity of carbonic anhydrase.

5. *Theory of Haldane.*—The theory to account for these various chemical changes in the blood which, for the main part, is now generally accepted is that suggested by Haldane (37), which really is a modification of that first proposed by Douglas, Haldane, Henderson, and Schneider (19). Haldane postulated that the hydrogen-ion concentration of the blood was delicately regulated by means of the respiration, the kidneys, and the liver. He considered that the respiration did the more rough and immediate regulation by increasing or decreasing the elimination of the carbon dioxide and that the kidneys and liver did the more delicate and painstaking work by adjusting fixed alkalies and acids. It has been shown since, of course, that ammonia is formed not in the liver but chiefly in the kidney.

The stimulation of the respiratory center produced by the anoxia causes a greater amount of carbon dioxide to be washed out of the alveoli of the lungs and, consequently, out of the arterial blood. This withdrawal of carbon dioxide produces an abnormal alkalinity of the blood. The kidneys and the tissues of the body slowly redress the balance—the kidney by excreting the excess alkali, and both the latter and the tissues of the body by suppressing the accumulation of free ammonia.

6. *Evidence for Haldane's theory.*—There is considerable evidence which substantiates Haldane's theory. It is known that the respiration is stimulated by anoxia, and it is also known that the hyperpnea produced by anoxia reduces the alveolar carbon dioxide and, consequently, the carbon dioxide arterial tension.

There is also evidence that the kidneys and the tissues of the body at high altitudes help restore the hydrogen-ion concentration of the blood. In 1915 Hasselbalch and Lindhard (45) found that subjects who had as yet not become acclimated to high altitudes showed a reduction in the hydrogen-ion concentration of the urine; after acclimatization had taken place, however, there was a return to normal. They also found a relative decrease in the excretion of ammonia, but this remained low even after acclimatization. Other workers (16, 39, 44, 46) have confirmed the fact that during anoxic anoxia there is a noticeable diminution in the titrable acid and am-

monia output in the urine. Sundstroem (100) in 1919, obtaining the total acid-base balance of the body at low and high altitudes by constructing balance sheets of all the acid and basic elements in the food and in the feces and urine, found at high altitudes an increased output of base, which consisted largely of fixed alkalies. A decrease in ammonia was also found, which Sundstroem explained as a corollary to the decreased elimination of fixed acids.

Y. Henderson has stressed the fact that the tissues of the body play the most important part in this compensatory process, and he has written:

> The first reaction to decreased oxygen is the increased breathing, which decreases the carbonic acid in simple solution in the blood, and leaves the blood slightly more alkaline than normal. The alkali then falls through some compensatory process, chiefly in the tissues, that keeps the concentration of hydrogen ions (pH) in the blood nearly the same as that which is normal at sea level. What this process in the tissues is, we do not know. But the volume of the tissues is so large in comparison to the volume of the blood that no considerable alteration in their acid base balance need be involved [55].

There appears to be clear-cut evidence, then, that the hydrogen-ion content of the blood resulting from the loss of carbon dioxide at high altitudes is practically restored to equilibrium by the respiration and by the action of the kidneys and the tissues of the body. It is also generally accepted that in inhabitants of high altitudes there is a reduction in the total alkalinity of the blood, that is, in the alkaline reserve.

In summary, then, the hemato-respiratory chain of events which occurs at high altitudes may be put in outline form as follows: oxygen lack—stimulates respiration—pulmonary ventilation is increased—production of alkalosis—depression of breathing—kidney eliminates fixed base and so acts as a compensatory mechanism—the kidneys (and perhaps other tissues of the body) suppress accumulation of free ammonia (which also acts as a compensatory mechanism)—hydrogen-ion concentration of blood kept in reasonable equilibrium.

The chain of events just outlined is true, of course, within certain physiologic limits; if the anoxia becomes too severe, a fatal degree of acidosis develops (p. 61).

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MOUNTAIN SICKNESS AND ALTITUDE SICKNESS

MOUNTAIN SICKNESS

It has been known for a long time that ascent to a high altitude often produces illness; the typical symptoms are: nausea, vomiting, headache, physical and mental depression, and gastrointestinal disturbances.

The symptoms of mountain sickness have been described in some detail by various authors: Mosso (23*), Barcroft[1] (3, 4), Haldane and Priestley (16), Monge (21, 22), and others writing on the physiology of high altitudes. This subject, too, has received considerable attention by various authors in treatises on mountaineering (12, 13, 17, 19).* The reader is referred to these sources for many details concerning this interesting subject.

A considerable individual variation exists in the ability to withstand oxygen want, as has been emphasized repeatedly; and this is especially true when applied to the possibility of suffering from mountain sickness. Some individuals are affected at a relatively low altitude, such as 7,000 or 8,000 feet, while others are comparatively immune. It has been said (1) that an elevation of 10,000 feet may produce symptoms in some subjects, while others may escape symptoms up to 14,000 feet; very few, however, can venture to a height of 19,000 feet without showing marked symptoms of mountain sickness.

Mountain sickness may manifest itself suddenly when the subject has gone too far beyond the critical line for him. An example of this is the mountain sickness which some tourists experience on Pike's Peak or that which is experienced by some passengers in airplanes flying at high altitudes. On the other hand, mountain sickness may

* See p. 138 for bibliographical references.

[1] A detailed account of mountain sickness which occurred among members of the South American party led by Barcroft in 1921–22 may be found in his monograph *The Respiratory Function of the Blood* (Cambridge University Press, 1925), Part I, "Lessons from High Altitudes." The reader is referred to chapters i and vii for a review of the subject.

develop more slowly. The subject first experiences a feeling of exceptional well-being but soon shows signs of cyanosis and experiences some premonitory symptoms, such as a feeling of dizziness when stooping over. In a few hours a feeling of lassitude appears. Toward evening a headache may develop, followed by a restless and troubled sleep. On awakening in the morning he suffers from a bad frontal headache and shows the symptoms of acute mountain sickness which have been listed in the preceding paragraph. There may be not only nausea and vomiting but other gastrointestinal disturbances; the tongue becomes furred, there is a loss of appetite, and diarrhea and abdominal pain sometimes develop. Some subjects complain of sensations of cold. In fact, the symptoms are very much like an acute attack of migraine. There may also be a tendency to periodic breathing, and at times hyperpnea accompanies physical exertion.

McFarland (20) recently has reported that the ten most commonly observed physiological changes, in order of frequency, in members of the International High Altitude Expedition to Chile were as follows: (1) shortness of breath on exertion and easy fatigability, (2) breathing irregularities, (3) cold extremities, (4) dry skin, (5) disturbed sleep, (6) gas in stomach or intestine, (7) headache, (8) sore throat, (9) irregular pulse, and (10) lassitude.

Interestingly enough, McFarland also pointed out that the following symptoms, which are frequently mentioned in the literature, seldom occurred: marked sensory impairment; nose bleeding; loss of appetite; nausea, tremors, and muscular impairment. It must be remembered, however, that the observations made by the members of this expedition were obtained from a small number of subjects (ten) and from a highly selected group.

Barcroft (3) pointed out that after the acute symptoms of *soroche*, the South American term for acute mountain sickness, had subsided, cyanosis remained in some degree in members of his South American party. Other aftereffects of low oxygen want also manifested themselves, such as some retardation in mental processes, as shown by the repeated errors made in performing routine laboratory experiments and by difficulty in using the slide rule and in the use of logarithms. In fact, both the mental and the physical factors were impaired to some extent in all or nearly all members of the party.

High-altitude disease.—Monge (22) in 1932 described what he termed "high-altitude disease," which subsequently has been called "Monge's disease." He classified this disease into two types: (1) the erythremic type, which he called "high-altitude erythremia," since the symptoms resembled those of Osler-Vaquez disease; and (2) the emphysematous type, in which the respiratory symptoms are more marked.

1. High-altitude erythremia: According to Monge, this type may appear in one of two forms: (*a*) the subacute type, which is mild; and (*b*) the chronic mountain sickness, which is severe.

a) Subacute type: The symptoms may appear insidiously; there is first a feeling of generalized fatigue, which bears no relation to the amount of work performed. Other symptoms are: cyanosis (produced by the least effort), cephalalgia, tendency to sleepiness, periodic type of breathing, and a marked congestion of the mucous membranes of the eyes, ears, and nose. Digestion is impaired, and the subject loses weight. If the patient continues to live in high altitudes, the symptoms often become worse, and nausea, vomiting, and dizziness appear, as well as troublesome paresthesias. The red blood cell count is generally about 7,000,000 per cubic millimeter, and the hemoglobin is increased from 10 to 20 per cent. The disease may disappear spontaneously, which means that complete acclimation has taken place. If this does not occur, the symptoms become aggravated, and the patient suffers from the second type, or chronic mountain sickness.

b) Chronic mountain sickness: This is a serious disease, and unless the afflicted subject moves to lower altitudes he may die. The symptoms are, for the main part, similar to those already described under the subacute type, but they are more severe; the cyanosis, for example, may be so pronounced that the face is purple or almost black; the tendency to sleep is more marked; and, in severe cases, the subject may fall into a coma for several hours. In addition to the symptoms enumerated under the subacute type, there may be a clubbing of the fingers, and the hands often become large and engorged with blood. There is often aphonia and epistaxis. The dyspnea is profound, and the thorax becomes large and emphysematous. There also may be signs of cardiac insufficiency.

The nervous and mental symptoms are extremely annoying; the patient complains of severe algesias and paresthesias, which may occur in almost any portion of the body. Mentally there may be an entire change in the personality. Monge gave an instance of an engineer who suffered crises of mental confusion at which time he made gross errors in drawing and in his mathematical computations. Often the subjects become indifferent and apathetic, and Monge cites an example of a subject who refused to go down to sea-level and finally had to be taken down in a comatose condition. The red blood cell count may be about the same as in the subacute type, namely, 7,000,000 cells per cubic millimeter.

In severe cases the patient will die unless he is taken down to sea-level. If he remains at a low altitude for a while, he can return to the high regions again; but once the disease manifests itself, it is apt to recur with increasing severity, so that more frequent trips must be made to lower levels and longer sojourns made there. In some instances the subject can no longer reside at high altitudes. If he persists in remaining in high altitudes, death is caused from hemorrhage, pulmonary thrombosis, bronchopneumonia, or progressive cardiac insufficiency.

2. Emphysematous type: The pulmonary symptoms predominate in this type of mountain sickness, as previously mentioned. As a rule, the patient has a long history of bronchitis; dyspnea is the major symptom and is produced by the least effort. Cyanosis is pronounced, and sometimes there is hemoptysis. The thorax is globular in shape, and the vital capacity is diminished. There may be an insufficiency of the right heart and a clubbing of the fingers—in short, a rather characteristic picture of a chronic emphysematous condition.

It is seen that high-altitude disease produces protean manifestations. Monge points out that the predominance of any one symptom is doubtless due to the fact that the particular organ involved suffers the most from oxygen want. Lastly, he feels that high altitude sickness is a distinct nosographic entity, since all symptoms disappear as soon as the patient reaches sea-level.

Cause of acute mountain sickness.—It was first pointed out by Paul Bert (5) that the essential cause of mountain sickness was pro-

duced by the lowered partial pressure of oxygen in the lungs. His theory, however, was challenged by Longstaff and also by Mosso. Longstaff ascribed the symptoms of mountain sickness to a combination of physical fatigue and a poverty of diet. He wrote a treatise expounding his views, called *Mountain Sickness and Its Probable Causes* (London, 1906). Filippi (12) held virtually the same view.

Mosso (23), the Italian physiologist, thought that at high altitudes carbon dioxide left the body in some unknown manner and that this caused mountain sickness. This was called the "acapnia theory" and enjoyed wide acceptance for some time.

It is of interest that recently Dill, Edwards, and Robinson (9) produced some evidence which supported Mosso's original theory, that the loss of carbon dioxide from the body at high altitudes played an important part in mountain sickness. These investigators allowed subjects to breathe, at a total pressure of 435 mm. Hg, a mixture containing enough oxygen to cause it to exert a partial pressure of about 90 mm. Hg. The arterial carbon dioxide tension was found to be lower than when the subjects breathed mixtures containing oxygen at a similar partial pressure but at sea-level. Dill *et al.* felt that this could not be explained as due to a difference in pulmonary ventilation or in oxygen consumption but that carbon dioxide actually left the blood more readily at low barometric pressures, as first claimed by Mosso. One reason they ascribed for the difference was that at low barometric pressures better mixing of the alveolar and dead-space air takes place.

Neither Longstaff's nor Mosso's theory, however, is now generally accepted. The present concept is that it is the lowered partial pressure of oxygen in the lungs which is the essential factor in the production of mountain sickness. This was the original view expressed by Paul Bert.

There are other factors which may play a part in the production of mountain sickness. One is the psychic element; it is hard to evaluate how important this is, but it probably plays a more important role than is generally recognized. The sight or smell of food, for example, often produces nausea at high altitudes much as it does in passengers on board ship.

Any factor which lessens the blood supply to the brain may aid

either in bringing on a bout of mountain sickness or in accentuating one already present. Exercise, which causes the blood to go to the muscles, and eating, which causes it to go to the splanchnic area, are thought capable of playing such a role.

There are, moreover, more subtle factors not thoroughly understood which may influence mountain sickness. A number of observers have noticed that mountain sickness varies in incidence in locality even though these localities are at the same approximate altitudes. Zuntz (27) long ago pointed out that this was an important consideration. He made the statement that mountain sickness occurred at 3,000 meters (9,842 feet) in the Alps and the Caucasus, 4,000 meters (13,123 feet) in the Andes, and 5,000 meters (16,404 feet) in the Himalayas. Some authors would doubtless question the validity of this and would quote different experiences; but, nevertheless, many writers agree that the chance of suffering from mountain sickness varies in different localities, although the altitudes are approximately the same.

Still other factors have been mentioned from time to time which may influence either the severity of the attack or its production; among these are: wind, weather, and the incidence of ice or snow on the rocks or their barrenness. These and more have been mentioned in the literature of mountaineering.

Although the main cause of mountain sickness, as has been mentioned, is due to the lowered partial pressure of oxygen in the lungs, there may be other factors as well. At any rate, there has not been given, as yet, a complete and satisfactory explanation for its occurrence. It was postulated by Barcroft (3) that mountain sickness is produced by the effect of oxygen want on the brain. On the other hand, he at one time mentioned that the vomiting is produced by lack of acid in the blood, which stimulates the vomiting center; on this account he urged the subject to engage in physical exercise, so as to raise the acid content of the blood. In view of the work of Edwards (10), previously quoted, this last suggestion would be of no avail.

It has been suggested by Haggard and Henderson (14) that their "respiratory *X*" (p. 150) causes the symptoms of mountain sickness. It first produces excitement, which they liken to that of the

excitement stage produced by ether inhalation; later its effects resemble alcoholic intoxication.

Haldane, Kellas, and Kennaway (15) have expressed the view that mountain sickness is probably due to a combination of anoxia and alkalosis. They felt that if the kidneys were able to eliminate the excess of blood alkalies quickly, the subject's tolerance to withstand high altitudes would be greater.

Sundstroem (25) found in himself an alkalosis of the blood during an attack of mountain sickness; in the afternoon of the same day that his attack subsided, he found a normal hydrogen-ion concentration. He, too, felt it was likely that mountain sickness might be explained on the inability of the kidneys to respond sufficiently quickly to the excess of bases in the blood.

It is pertinent that it has been observed (7, 18, 24) that inhalation of proper dilutions of carbon dioxide reduces the symptoms of mountain sickness. This points to the theory that alkalosis may play an important part in its development. It is also proper to recall that Barcroft long ago suggested that the production of acid should be encouraged if an attack of mountain sickness seemed pending. On the other hand, the ingestion of ammonium chloride (p. 147), which is known to produce an acidosis, has given rather disappointing results in combating the development of mountain sickness. The problem, therefore, is apparently not so simple.

Finally, it may be said that the mechanisms actually responsible for acute mountain sickness are not, as yet, thoroughly understood but that they are probably associated with chemical changes in the body brought about by the low oxygen pressure. A complete explanation of the cause of mountain sickness cannot be given until the exact nature of these changes is known.

Cause of chronic mountain sickness.—The cause for chronic mountain sickness is quite unknown, but it has been suggested by Talbott and Dill (26) that the symptoms may be due to pathological changes occurring in tissues which have been exposed to oxygen want for a long time; but they also suggest that the abundant ultraviolet rays at high altitudes may be responsible for this condition.

Sickness produced by types of anoxia other than anoxic.—While anoxic anoxia produces what is generally understood as "true moun-

tain sickness," other types of anoxia can produce symptoms which, in many ways, resemble it. In stagnant anoxia, such as that produced by circulatory disturbances, the patient often shows signs of nausea and, in severe cases, even vomiting. Intestinal disturbances are also manifested, and a feeling of lassitude and weakness, as well as a physical and mental depression, is exhibited.

In the anemic type of anoxia, such as that produced by pernicious anemia, disturbances similar to those described under stagnant anoxia may develop. The anemia must be very severe, however, before grave symptoms occur. Later, when the nervous system becomes involved, owing to the lack of oxygen, there may be great muscular weakness and inco-ordination. These symptoms, however, are caused by the organic changes produced in the central nervous system; so, in this respect, they differ from those produced by the anoxic type.

The symptoms produced by histotoxic anoxia fall into a somewhat different category. Cyanide, of course, produces an intense stimulation of the respiratory center, and hyperpnea is the most noticeable symptom. Alcohol, which is generally considered a histotoxic agent, produces many of the symptoms observed in the anoxic type. If taken in excess, nausea and vomiting result; this, however, is caused by local irritant action. It also produces headache, lassitude, and physical and mental depression.

ALTITUDE SICKNESS

Armstrong[2] in his recent book (2) mentions that Schneider in 1918 suggested that the term "altitude sickness" be used to designate illness produced by flights at high altitude, to differentiate it from "mountain sickness." Armstrong has pointed out, however, that two forms of "altitude sickness"—acute and chronic—must be recognized. Altitude sickness is produced by breathing air containing a low partial pressure of oxygen and is brought about during aircraft flights at high altitudes.

[2] For a detailed discussion of altitude sickness the reader is referred to chapters xvii and xviii of Captain H. G. Armstrong's book, *Principles and Practice of Aviation Medicine* (Baltimore: Williams & Wilkins Co., 1939). The author of this monograph has drawn freely on these two chapters for the discussion concerning altitude sickness.

Acute altitude sickness.—It has been stated (2) that in young, healthy male adults the first significant changes which occur in the body from altitude disease are at about 9,000 feet. At a rate of ascent of 1,000 feet per minute the subject will become unconscious at an altitude of about 25,000 feet. Table 13 gives the subjective symptoms which occur, in the order of their frequency.

Objective symptoms.—The effects of acute anoxia on the various organs are responsible for the objective symptoms manifested in acute altitude disease. These effects are considered in their appropriate places throughout this monograph and need not be repeated here.

TABLE 13

SUBJECTIVE SYMPTOMS OCCURRING IN ORDER OF FREQUENCY DURING FLIGHTS AT HIGH ALTITUDES*

12,000 Feet	14,000 Feet	16,000 Feet
Sleepiness	Headache	Headache
Headache	Altered respiration	Altered respiration
Altered respiration	Sleepiness	Psychologic impairment
Lassitude	Psychologic impairment	Euphoria
Fatigue	Lassitude	Sleepiness
Psychologic impairment	Fatigue	Lassitude
Euphoria	Euphoria	Fatigue

* From Armstrong's *Principles and Practice of Aviation Medicine* (Baltimore: Williams & Wilkins Co., 1939), p. 265.

Aftereffects.—Armstrong states that prolonged passive exposure at altitudes less than 9,000 feet or momentary exposures up to 25,000 feet produce no distressing aftereffects. Headache and a sense of fatigue, however, usually follow a 3- or 4-hour flight at an altitude between 10,000 and 12,000 feet. If longer flights are taken or if higher altitudes are reached, these aftereffects are increased in intensity and duration.

Distressing symptoms such as intractable headache, nausea, and vomiting may be produced by flying at altitudes of 15,000–18,000 feet for several hours; other symptoms associated with acute anoxia, particularly mental confusion and muscular weakness, may also occur. At great altitudes, 24,000 feet or over, these symptoms sometimes appear within 15–20 minutes; when such severe symptoms are produced, they often last as long as 48–72 hours.

Death from acute altitude sickness is probably always due to failure of the respiratory center, which may occur at altitudes as low as 16,000 feet. At 25,000 feet death may occur within 20–30 minutes.

Chronic altitude sickness.—Chronic altitude sickness is produced by repeated aircraft flights to high altitudes, so that the subject is exposed repeatedly to air which contains a low partial pressure of oxygen. It is now known that repeated exposures to rarefied air have an accumulative effect on the body.

It was observed by a number of investigators (6, 8, 11) during the War of 1914–18 that airplane pilots who had made successive flights to high altitudes showed evidence of chronic fatigue, while those pilots who had used oxygen at high altitudes did not show these symptoms to such a marked degree.

Although it was understood, in a general way, that repeated exposures to high altitudes caused considerable disability in pilots, no well-controlled experiments were carried out on this problem until Armstrong and Heim (2) made a rather extensive study on the effect of repeated exposures to high altitudes in human beings. These authors subjected ten healthy college students to a simulated altitude of 12,000 feet in a steel chamber for 27 consecutive days (except Sunday). They were divided into two groups; one group was kept at this simulated altitude for 4 hours, and the other for 7 hours.

Subjective symptoms.—After the first few days the 4-hour group complained of mild headaches during the exposure, headaches which persisted for several hours afterward. Later, in the course of the experiment, the headaches were less frequent; but the subjects complained of sleepiness, a disinclination for activity of any sort, and a physical fatigue. During the third week they complained of increasing irritability, nervousness, insomnia, and other symptoms referable to the central nervous system.

The 7-hour group showed symptoms generally similar to those of the 4-hour group, but at the end of the first week of exposure they had additional complaints of mild attacks of nausea, anorexia, indigestion, and vertigo. These latter symptoms were obviously like those of mountain sickness.

These experiments reported by Armstrong and Heim definitely

proved that altitude sickness can develop from repeated exposures to altitudes as low as 12,000 feet.

Armstrong (2) also had an opportunity to study the effects of repeated exposure to oxygen want on pilots who were subjected several hours daily to altitudes of 12,000–16,000 feet for a period of from 1 to 6 weeks. These men complained that after a week or two they suffered from mental fatigue, lassitude, sleepiness, and pronounced irritability—that is, symptoms similar to those complained of by the members of the experimental group previously mentioned. It was found that the period of time necessary to recover completely from these effects was approximately equal to the time of exposure; that is, if they had been flying a month, a subsequent month of rest was required for recovery.

Objective symptoms.—The objective symptoms which were observed in the individuals who had been exposed to a simulated altitude of 12,000 feet for a number of days were: a slight drop in body temperature within 24 hours following their exposure; an increase in the urinary output; a slight loss of body weight; and a tendency toward a slow pulse after a few days' exposure and a slight drop in both systolic and diastolic blood pressure.

One of the most interesting observations was that the 7-hour group showed signs of acclimatization, as seen by the red cell count and the rise in hemoglobin; the 4-hour group, on the other hand, showed no signs whatsoever of acclimatization.

Certain psychological changes were also noted, such as mental and physical sluggishness, slight loss of muscular co-ordination, and a marked loss of inclination for mental and physical effort. Other symptoms referable to the central nervous system were also noted.

Finally, Armstrong has called attention to the fact that the symptoms of chronic altitude sickness somewhat resemble those of Addison's disease. He mentions that, although it has not been proved, the symptoms might possibly be due to cortico-adrenal insufficiency. Obviously, more work is needed on this interesting problem.

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ACCLIMATIZATION

Since the chemistry of respiration at high altitudes and also mountain sickness have been discussed, acclimatization may now be considered.

ACCLIMATIZATION TO HIGH ALTITUDES

The acute symptoms of mountain sickness, such as headache, nausea, vomiting, blurred vision, and other disturbances, disappear after a short residence at high altitudes, and later the chronic symptoms, too, become lessened. The disappearance or alleviation of these symptoms is brought about by the process of acclimatization. It is generally accepted that an unacclimatized subject can remain conscious to an altitude between 23,000 and 25,000 feet; on the other hand, acclimatized individuals may be reasonably comfortable and may even engage in physical exercise at altitudes between 26,000 and 28,000 feet.

It has been stated, previously, that the process of acclimatization is not understood in its entirety; while a good many facts are known concerning it, a great deal more research is needed to fill in certain gaps in our knowledge of this problem. Acclimatization consists of certain bodily responses involving the respiration, the blood, and the circulation and of certain chemical changes which may be regarded as compensatory mechanisms. Those responses which are generally recognized and for which there appears to be abundant experimental proof may be listed as follows:

1. An increase in the total ventilation of the lungs is produced by stimulation of the respiratory center (by reflexes from the carotid and aortic bodies, produced by oxygen want).

2. The hyperventilation produces a fall in alveolar carbon dioxide pressure with a concomitant increase in alveolar oxygen pressure, thus raising the oxygen pressure to which the blood in the lung capillaries is exposed.

3. The hyperventilation produces an increased blood alkalinity, since the carbon dioxide is blown off. The blood alkalinity, however,

is prevented from rising beyond certain limits by the increased excretion of alkalies by the kidneys.

4. There is an increased number of erythrocytes, first by contraction of the spleen and later by a stimulation of the redbone marrow.

5. The hemoglobin in the blood is increased in percentage and in total amount, so that more oxygen may be carried in the blood.

6. There is an acceleration of the heart rate, an increased cardiac output, and perhaps other changes in the circulation which are thought to increase the volume of blood flow and to raise the oxygen pressure in the tissues.

7. In the natives born and reared in high altitudes there is a noticeable enlargement of the chest, which gives then a greatly increased vital capacity.

Next may be mentioned those responses which are not so generally recognized and which require more experimental proof to establish the importance of their role in adaptation to low oxygen want.

1. Natives at high altitudes have been found to have abnormally large erythrocytes (41*); there is less hemoglobin in each red cell than at sea-level, but the surface over which the hemoglobin is exposed is unusually large, which facilitates the gaseous exchange in the lungs and tissues.

2. There may be an increase in myohemoglobin (44).

3. A cardiac hypertrophy may take place in high altitudes.

4. There may be an unknown tissue factor in acclimatization; that is, in some unknown way the tissues may become adapted to function well at a lower level of oxygen pressure.

5. The increased blood alkalinity is said to cause a greater affinity of the hemoglobin for oxygen (5). The dissociation curve is thought to be shifted to the left.

6. A dilatation of the lung capillaries and a dilatation of the lung alveoli may take place at high altitudes.

The first seven generally recognized factors listed have been discussed in detail in their appropriate places. The others, however, need further elucidation and will now be considered.

* See p. 156 for bibliographical references.

Large erythrocytes at high altitudes.—Hurtado (41) found the erythrocytes abnormally large in the Peruvian natives at an altitude of 14,890 feet; but, while these large red cells contained less hemoglobin than at sea-level, the surface offered by these cells was unusually great. He deemed this latter point very important.

As far as the blood morphology is concerned, Hurtado does not think the increase in red cell count and hemoglobin the important factors in adaptation to high altitudes, but rather a fine and close correlation between cell number, volume, and hemoglobin and also the existence of a large surface area in the individual erythrocytes for hemoglobin and oxygen content which favor the proper supply of this gas to the tissues. He feels that this last process probably is the basic and fundamental problem of adaptation to high altitudes.

Increase in myohemoglobin.—Myohemoglobin may be regarded as a respiratory pigment, and its probable function is to store oxygen to be used by the muscle. It has been suggested (8) that myohemoglobin may play an important part in adaptation to high altitudes. Hurtado and his co-workers (44) have reported that dogs born and reared at high altitudes may have twice the amount of myohemoglobin in a given tissue as dogs at sea-level. The diaphragm was found to have the greatest increase.

It has been pointed out by Dill (18) that the unusual abundance of myohemoglobin in the diaphragm may account for the fact that this muscle is so efficient in the ventilation of the lungs during anoxia; that is, the respiratory pigment gives the muscle effective means of oxygen utilization.

It is evident that more study is needed on the physiology of this pigment and its relation to the process of acclimatization. It may offer a fruitful field for biochemical research.

Cardiac hypertrophy during anoxia.—It has been suggested (40) that cardiac hypertrophy may be a factor in the process of adaptation to oxygen want. The interpretation is that a hypertrophied heart is a stronger heart and is better able to pump the blood around the body and so supply the tissues more adequately with oxygen. As far as the author is aware, however, there are no reliable data indicating that inhabitants in high altitudes show a significant cardiac hypertrophy. There is, moreover, a divergence of opinion whether or

not a hypertrophied heart is necessarily a stronger and more efficient one. (The reader is referred to page 77, which deals with the heart under anoxic condition.)

Unknown tissue factor; ability of cells to accustom themselves to function at lower oxygen pressure.—Paul Bert first called attention to the possibility of cells accustoming themselves to function at a lower oxygen pressure as a possible factor in adaptation to oxygen want; since his time, nearly all authors writing on this subject have mentioned it also. Indeed, it seems quite worthy of consideration, although, thus far, no proof has been presented that cells may actually accommodate themselves to function normally at lower oxygen pressure. It may be, however, that in some unknown way the tissues become adopted to a lower partial pressure of oxygen than that to which they were formerly accustomed and carry out their functions reasonably well.

Haldane (28) stated that the best evidence we have that tissues may adapt themselves to a lower partial pressure of oxygen is shown in certain cases of congenital heart defects; in these conditions the tissues have to function under an extraordinarily low oxygen pressure. (For a specific example of this see "Acclimatization in Disease," p. 155.)

It may be pointed out that habit plays a very important part in the normal function of the central nervous system. This is so well known that it needs no further emphasis. It is possible that the tissues of the body, including those of the central nervous system, may change their fundamental processes so that they may function well at a lower partial pressure of oxygen. An instance may be mentioned which indicates that cells may change their habits. It is known that less food is needed to keep the body in equilibrium after the body has undergone a long period of semistarvation. It appears that the body cells adapt themselves to function well at lower metabolic levels.

Oxygen dissociation curve of the blood during acclimatization; question of increased affinity of hemoglobin for oxygen.—The question of increased affinity of hemoglobin for oxygen at high altitudes already has been discussed (p. 52). It will be recalled that, in contrast to the findings of other workers, Barcroft (5) reported that on the An-

dean Expedition of 1921–22 evidence was found at an altitude of 14,200 feet that the oxygen dissociation curve of the blood of the members of the expedition shifted to the left, indicating a gain in the affinity of the hemoglobin for oxygen. Although, while recent work (19, 47) has failed, in part, to support this view, nevertheless, Barcroft's theory will be considered briefly.

He has emphasized that at high altitudes the blood does not remain in the lung capillary long enough to reach approximate equilibrium with the alveolar air, or, as he put it: "The capillary is too short for the purpose." The shift of the dissociation curve to the left, however, increases the difference in oxygen pressure between the oxygen in the blood and that of the alveolar air. This difference in pressure obviously promotes more rapid diffusion of gas into the blood and makes it more nearly in equilibrium with the alveolar oxygen. The blood leaves the lung capillaries, therefore, supplied with a higher pressure of oxygen.

It is recognized by Barcroft that the greater affinity of the hemoglobin for oxygen in acclimatized individuals is not entirely to the advantage of the organism, since the blood holds the oxygen more tenaciously when it reaches the tissues. He feels that the advantages outweigh the disadvantages, inasmuch as the oxygen cannot get out of the blood until it first gets into it.

Dilatation of the lung capillaries and dilatation of the alveoli.—Hurtado (42) in 1932 made anatomical studies of the lungs of animals and natives living at high altitudes and observed that the capillaries of the lungs and the lung alveoli were dilated. It has been shown (10, 57) experimentally that oxygen want produces a marked pulmonary congestion and dilatation of the alveoli. Hurtado, Kaltreider, and McCann (43) believe that the dilatation of the alveoli found at high elevations should be regarded not as a pathological process but as an important compensatory mechanism, since the dilated alveoli provide a greater surface area for the diffusion of the respiratory gases.

Question of value of increased hemoglobin at high altitudes.—It is appropriate to point out that the value and importance of some of the compensatory mechanisms which have been given as being generally recognized are not entirely clear. One is the increase in hemo-

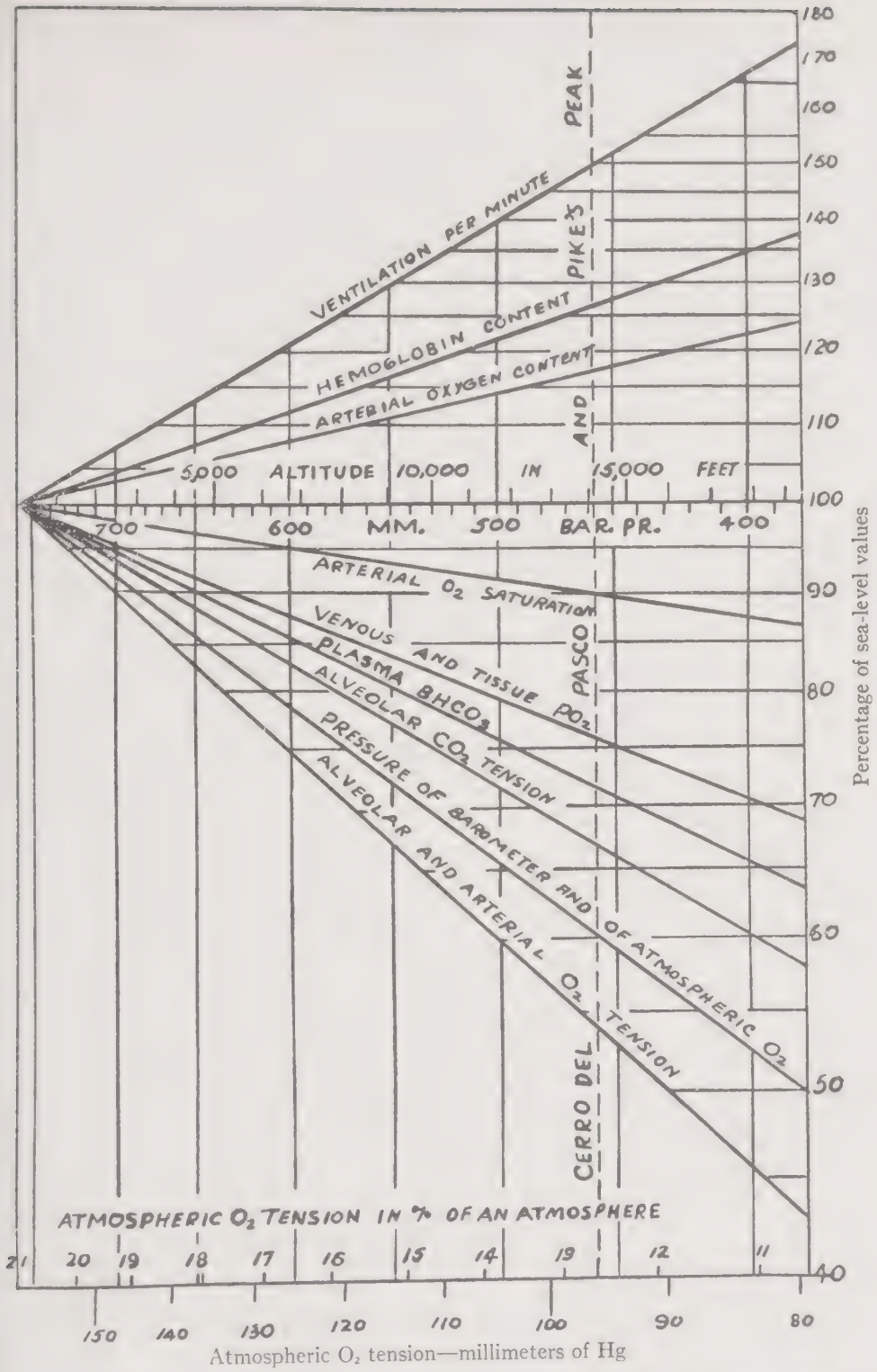

FIG. 9.—Effects of residence at high altitudes sufficiently long for acclimatization. The values are plotted logarithmically in order that a given distance either above or below the central horizontal line shall indicate the same proportional change from sea-level values. Ventilation and alveolar CO_2 tension change inversely in like proportions and both lag about 14 per cent behind barometric changes. The alveolar pO_2 falls by the same margin more rapidly than the barometer, because the lag of respiratory acceleration behind barometric fall permits a larger percentage of reduction to occur in the pO_2 of the atmospheric air before it is exhaled. (From Peters and Van Slyke, *Quantitative Clinical Chemistry* [Baltimore: Williams & Wilkins Co., 1932], I, 573.)

globin known to accompany sojourns at high altitudes. Barcroft (3) has deemed that the increase may be of no great value since, even though the increased hemoglobin restores to normal the actual quantity of oxygen to a given unit of blood, the concomitant decrease in oxygen pressure causes the rate of dissociation to be so slow that it does not allow the normal amount of oxygen to pass to the tissues. As Barcroft has stated: "It is not the deficiency of actual quantity of oxygen in the blood which is the cause of the trouble in the mountains, it is a deficiency of the pressure at which the oxygen is transferred" (6). While this doubtless is true, it may be pointed out that, since there is a greater total oxygen content, more of it, than otherwise, can be removed for perfusing the tissues without changing the oxygen tension.

Haldane (33) has stated that the value of the increased hemoglobin lies in the fact that it prevents the partial pressure of oxygen in the blood of the systemic capillaries from falling too low. Although, as just mentioned, Barcroft once wrote that he deemed the increase of hemoglobin of no great value, in his monograph (4) he, nevertheless, considers in some detail how an increase in the quantity of hemoglobin leads to an increase in the average oxygen pressure in the capillaries.

In 1928 Campbell (11) reported that an increased amount of hemoglobin at high altitudes was of no benefit to the organism. The experimental method he used, however, has been criticized by Haldane and Priestley (33).

Dill (17) believes that it is possible that the advantages of the increased amount of hemoglobin may outweigh the disadvantages, although he points out that, when a man goes to a low altitude after a high hemoglobin concentration has been reached at high altitude, there is no evidence of unusual capacity for muscular work. He emphasizes further that the mean value for hemoglobin concentration in distance runners is about the same as in the ordinary man and, lastly, that patients suffering from polycythemia vera are actually relieved by blood-letting. Certain theoretical objections may be raised, however, to the validity of these arguments.

Polycythemia not always present at high altitudes.—Another finding difficult to reconcile with the usual concept of acclimatization is that

not all residents of high altitudes show an increase in the number of red blood cells. Hurtado (41) has reported several such instances in men living at altitudes between 14,000 and 16,000 feet, and Dill reports such a finding in an individual residing at 17,500 feet in the Chilean Andes. These findings, together with certain other observations, have led Hurtado, as previously mentioned, to conclude that an increase in the erythrocytes is not an important factor in adaptation to oxygen want.

The question of acclimatization during discontinuous exposure to low barometric pressures.—Haldane, Kellas, and Kennaway (31) studied the effect of exposure of 6–8 hours to barometric pressures of 500, 430, and 360 mm. Hg (corresponding to 11,000, 15,000, and 19,000 feet) on three successive days. It was found that the carbon dioxide alveolar pressure returned to normal before morning after each successive exposure. While there was no lasting adjustment of blood reaction or lasting increase in the hemoglobin percentage, it was felt that there was a certain amount of acclimatization.

It has been postulated by Haldane and Priestley (32) that, if airmen are in good health and ascend to high altitudes rather often, they probably acquire some degree of acclimatization, but probably an equal degree of acclimatization can be obtained by good physical training. These authors have stated also that but little difficulty should be experienced by airmen from anoxia up to an altitude of 20,000 feet if they are in good physical training. Many authors doubtless would take issue with this statement.

In this connection it is of interest to present the findings of Armstrong and Heim (2). While they found some evidence of acclimatization in subjects who were exposed daily to a simulated altitude of 12,000 feet for a period of 7 hours, no evidence of adaptation was found in a group who had been subjected to this altitude for 4 hours daily. These authors drew the conclusion that the generally accepted theory, that airplane pilots become adapted to altitude through repeated exposures, is in error.

Hastening of acclimatization; ingestion of ammonium chloride.—It is known that hyperventilation produced by oxygen want causes an alkalosis, and it is believed by some that this is responsible for mountain sickness. There is some experimental evidence that, as soon as

the excess alkali can be gotten rid of by the kidneys, the subject recovers from his mountain sickness and is beginning to become acclimatized.

It has been postulated that if a mild state of acidosis could be produced mountain sickness might be avoided and acclimatization brought about more readily. It is known that the ingestion of large amounts of ammonium chloride will produce an acidotic condition in the body. J. B. S. Haldane (27) took large amounts of ammonium chloride during 2 or 3 days, and an abnormal amount of ammonium chloride was found in his blood. A marked fall in the available alkali of the blood occurred, and there were pronounced respiratory and other symptoms of acidosis; the urine, too, became very acid.

Several investigators have reported on the effect of the ingestion of ammonium salts on mountain sickness and acclimatization. In 1923 Adlersberg and Porges (1), making observations on the Jungfraujoch (11,343 feet), reported that the ingestion of acid ammonium phosphate increased alveolar oxygen tension and oxygen saturation of the capillary blood. In 1932 Greene (25), in the expedition made to Mount Kamet, thought that beneficial effects were derived from taking small doses of ammonium chloride. A year later Douglas *et al.* (20) investigated the matter experimentally. At a barometric pressure of 347 mm. Hg (20,000 feet) in a steel chamber they compared the general condition and capacity to do muscular work after the ingestion of ammonium chloride. The subject showed a lower alveolar carbon dioxide pressure and a higher oxygen pressure after treatment with this salt. The cyanosis appeared to be less, the pulse slower, and there was a greater capacity to do muscular work. They concluded that the administration of ammonium chloride definitely accelerated the process of acclimatization to low barometric pressure.

Other workers, however, have reported less encouraging observations. In 1937 Barron *et al.* (8) administered ammonium chloride (15 gm.) to six of twelve men who ascended by automobile to an elevation of 15,600 feet within a period of 8 hours. They concluded that the ingestion of this salt was more of a handicap than an advantage, since three of the six men who took it had severe mountain sickness, while of the six men who served as controls only two were similarly affected.

It appears, then, from the available evidence that the value of the ingestion of ammonium salts for the prevention of mountain sickness is questionable and that more carefully controlled work is needed before conclusions may be drawn.

Ingestion of sodium bicarbonate and potassium chlorate.—Besides the ingestion of ammonium chloride to hasten acclimatization, sodium bicarbonate and potassium chlorate have been used. In the belief that during an ascent to high altitudes an acidosis of the blood is produced, sodium bicarbonate has been administered but apparently without any success. Whymper (60), on Mount Chimborazo (20,500 feet), swallowed some potassium chlorate, reasoning that it would provide an extra amount of oxygen. Since this compound, however, converts hemoglobin into methemoglobin, it probably decreased the oxygen-carrying capacity of the blood.

The inhalation of a little carbon dioxide.—In order to increase breathing, the inhalation of a little carbon dioxide has been tried to hasten acclimatization. According to Henderson, the results obtained by him and his collaborators (15) on Pike's Peak suggest that carbon dioxide might improve the conditions of persons suffering from mountain sickness and might be of some use for aviators between 10,000 and 15,000 feet.

In summary, it may be said that none of these substances mentioned have proved to be a substantial aid in hastening acclimatization. Henderson (39) has well stated: "Acclimatization to a great altitude involves a functional adjustment that is gradually acquired and as gradually lost. It is not to be gained by swallowing some ammonium chloride. Nor can it be reversed by a dose of sodium bicarbonate."

Increased resistance to oxygen want in animals on certain diets.—In 1938 Campbell (14) reported that rats fed on a pure carrot diet showed a definite protection against acute oxygen want. He suggested that the carrots must either contain some substance which opposes oxygen want or lack some factor or factors which enhance oxygen want. It was further suggested that these experimental findings might be of some clinical significance, since it might be possible to work out a diet which would be beneficial for patients suffering from oxygen want.

Cause of low alveolar carbon dioxide tension and greater ventilation of lungs after acclimatization.—The physiologic value of a greater ventilation after acclimatization is not in dispute, but the mechanism is not clear. Several investigators have offered divergent theories explaining this phenomenon.

Barcroft (4) has stated that at any altitude above sea-level there is in the blood a slight increase in acid. He explains that this slight increase of acid is sufficient to stimulate the respiratory center and, in this way, accounts for the increased ventilation. A slight acidosis of the blood, after successful acclimatization, has been reported by Sundstroem (59), which lends support to this view.

Hasselbalch and Lindhard (35) maintain, however, that after acclimatization there is no change in the hydrogen-ion concentration of the blood at any altitude. They ascribe the increased breathing as being due to the abnormal sensitiveness of the respiratory center to the hydrogen ions.

Haldane (30) has expressed the view that there is a slight alkalosis after acclimatization, which shows that there is a continuous slight oxygen want, permitting the action of diminished oxygen want on the respiratory center.

Haggard and Y. Henderson (26) postulated an unknown substance, which they called "respiratory *X*," that is formed by the action of the low oxygen/alkali ratio. They feel that it is this "respiratory *X*" that stimulates the respiratory center. Their defense of their "respiratory *X*" is that it is insufficient to say that oxygen want stimulates or governs the excitability of the respiratory center for carbon dioxide, since it does not state how it is done. Recently, Henderson (37) has stated that, while it is not known what hyperpnein (or "respiratory *X*") is, presumably it is a substance produced in the muscles, and perhaps in other tissues as well, under intense exertion or oxygen want. He suggests that it probably acts not on the respiratory center but through the nerve endings in the carotid sinus. The "respiratory *X*" described by Henderson, however, has never been universally accepted.

Henderson (36) feels that after acclimatization the blood is set at a degree of acarbia corresponding to the oxygen pressure at that

particular altitude and that for every altitude there is a definite degree of acarbia.

In summary, it seems, then, that there is no general agreement as to the exact cause of a greater ventilation of the lungs after acclimatization. Several theories seem to hinge on the point whether or not, following acclimatization, there is a slight alkalosis or an acidosis of the blood. Obviously, more carefully controlled data are needed to establish this point.

Lowest oxygen tension at which acclimatization can take place.—It has been observed by a number of workers that beyond a certain critical altitude animals will not eat, which means, of course, that they quickly lose weight and die. Campbell (13) in a series of papers has presented evidence that animals cannot acclimatize fully to 10 per cent oxygen or less (equivalent to an altitude of 20,000 feet). The criteria which he uses for full acclimatization are rigid but fair. They are: maintenance of growth in young animals, maintenance of body weight in mature animals, no loss in appetite, a feeling of general well-being, and normal fertility.

He found that if young animals were exposed beyond a critical altitude growth ceased, a progressive loss of weight ensued, and they eventually died of symptoms of chronic heart failure. At 12 per cent oxygen (equivalent to an altitude of 17,000–18,000 feet) the young animals, however, did grow. He feels that it is not reasonable to speak of true acclimatization above 20,000 feet, since at this altitude the problem is pathological and not physiological.

About the same conclusions were reached by the members of the International High Altitude Expedition to Chile (53), namely, that about 10.5 per cent oxygen (equivalent to an altitude of 17,500–18,500 feet) appears to be the limit to which man can become adapted permanently.

Expeditions to the Himalayas, especially those made for the purpose of climbing Mount Everest, have increased our knowledge concerning processes associated with acclimatization. It was proved that subjects may get along fairly well at extreme altitudes. A number of the members of these various expeditions could climb at altitudes well over 26,000 feet. Somervell, for example, felt quite comfortable at 26,000 feet, although his pulse was 180 per minute and

his respirations from 50 to 55 per minute (58). Although some of these men actually ate and slept at great heights, this does not mean that they ever could become adapted permanently to these altitudes.

It may be accepted, then, that at the present stage of evolution of mammals the process of adaptation to oxygen want is definitely limited. It is likely, moreover, that if in the course of evolution mammals learn to become acclimated to lower oxygen levels, it will be only by the relatively slow process that has characterized all changes of adaptation of an organism to a new or changed environment.

Dyspnea on exertion in acclimated man.—Even in well-acclimated individuals, exertion at high altitudes produces dyspnea. This is doubtless due to the fall in plasm bicarbonate. As a matter of fact, dyspnea may be produced experimentally by the ingestion of an acid salt, such as ammonium chloride (see p. 147). It is known, of course, that in the process of acclimatization the bicarbonates in the blood fall. According to Haldane (29), the fall in plasma bicarbonate is necessary to maintain an accelerated rate of the respiratory center at high altitudes. He has pointed out further that exercise at sea-level would be associated also with dyspnea if there were a similar fall in plasma bicarbonate. He maintains, therefore, that breathing oxygen does not increase the exercise tolerance of the acclimated mountaineer.

It is regarded by some that the dyspnea on exertion at high altitudes acts as a safeguard and protects the mountaineer from overexerting himself and thus actually producing involuntary suicide. It is known that oxygen deficit comes on insidiously and often without any warning; death at high altitudes can thus be caused by great exertion, especially in the unacclimated. Even the acclimated individual is found not to be immune, and cases have been reported of sudden death of these individuals after severe exertion (Mount Everest expeditions, Sven Hedin travels, etc.).

Acclimatization to carbon monoxide.—Man and animals may become acclimatized not only to air containing a low partial pressure of oxygen but also to air which contains small amounts of carbon monoxide. This is not unexpected, since it is thought that, for the main part, carbon monoxide produces an anemic type of anoxia.

a) Acclimatization in animals: The first systematic examination

of acclimatization of animals to carbon monoxide was made by Nasmith and Graham (54) in 1906. These investigators found that guinea pigs kept continuously in a diluted carbon monoxide atmosphere showed an increase in the quantity of hemoglobin and in the number of red blood cells. The blood, therefore, had increased its oxygen-carrying capacity. It has been shown by Campbell (12) that mice acclimatize slowly to atmospheres containing about 0.30 per cent carbon monoxide (30 parts per 10,000) and, further, that rabbits, rats, mice, and guinea pigs, after acclimatization produced by continuous exposure to carbon monoxide, could tolerate a much higher atmospheric concentration of carbon monoxide than they could when unacclimatized. Killick (49) in 1937, working with mice, showed that acclimatization occurred, in that there was an absence of positive signs of poisoning. Animals exposed for the first time to the atmosphere in which the acclimated mice lived, and which contained carbon monoxide, collapsed very soon.

Killick (50) has emphasized that animals develop a considerable degree of acclimatization to carbon monoxide; and, in summing up the results of the experimental work, she points out that many of them show an increased production of red blood cells, a cardiac hypertrophy, an increase in the blood volume, and splenic enlargement. According to Killick, however, no evidence has been found indicating a change in the relative affinity of hemoglobin for carbon monoxide.

b) Acclimatization in man: It was pointed out as early as 1856 by Faure (22) that among those subjects whose work exposed them to carbon monoxide a certain amount of tolerance or acclimatization developed. Later writers (23, 55) also called attention to this phenomenon.

According to Killick (50), attempts to acclimatize human subjects to carbon monoxide have yielded conflicting results. It had been observed in 1896 by Haldane and Smith (34), who at that time were engaged in experiments which necessitated breathing a small amount of carbon monoxide, that after a certain length of time they became more resistant to it. In 1929 Sayers *et al.* (56) subjected individuals to repeated daily exposures to small amounts of automobile exhaust gas. The experiments extended over 2 months; the hemoglobin con-

tent of five of the six men increased; in four of the subjects there was an increase in the red blood cells; the greatest increase in the amount of hemoglobin was 30 per cent and in the red cell count, 1,000,000 per cubic millimeter. Killick (48) in 1936 reported somewhat similar studies on one human subject. She concluded that, as evidenced by the symptoms experienced, the subject developed a considerable degree of acclimatization. She found, however, no increase in the number of red cells or in the hemoglobin. She pointed out that the exposures to carbon monoxide had not been very frequent.

Several observers (9, 45, 46) have reported an increase in hemoglobin and number of red cells in the blood of men whose work involves exposure to carbon monoxide. Karasek (46) found an increase in the red cell count to as high as 9,680,000. On the whole, however, it is thought that the red cell increase is not so prominent a feature in human acclimatization as it is in animal experimentation. As a matter of fact, there are a number of points about human acclimatization to carbon monoxide which are not thoroughly understood. The reader is referred to the original articles of Killick, to which reference already has been made, and to the monograph of Drinker (21).

ACCLIMATIZATION TO CARBON DIOXIDE

A recent study has shown that animals may become acclimated to carbon dioxide. Miller (52) in 1940 made blood studies on dogs which had been exposed to atmospheres containing 1.5–5.0 per cent carbon dioxide. He found a mild uncompensated acidosis (pH 7.20–7.30) with a decline in carbon dioxide combining power. There was a decrease in the whole blood chloride and a transfer of chloride from plasma to erythrocytes.

An increase in the total leucocyte count was found, but there was no appreciable change in the differential count. There was, too, an increase in the number of erythrocytes and in the hemoglobin concentration. The rise in the reticulocyte count indicated that the bone marrow had been stimulated. The author concluded that the tissue anoxia, which resulted from depression of tissue oxidation by carbon dioxide, produced a stimulation of the bone marrow.

The work of this author shows that the changes produced in the blood by the increased carbon dioxide tension are similar to those

produced by anoxic anoxia. This is not unexpected, since in both cases there is some increase in tissue acidity and a decrease in tissue oxidations.

In evaluating the factors which are responsible for the adaptation of an organism to a low oxygen tension, it would seem unwise, in our present stage of knowledge, to insist that any one factor or any limited group of factors is the most important in the process of adaptation. The great individual variation which is known to exist would alone mitigate against this view; witness, for example, the fact that some subjects show no polycythemia even at extreme altitudes. It seems more plausible that the process of acclimatization depends upon a combination of factors, some of which are more important in some individuals than in others.

It must be remembered, also, that there is no general acclimatization; that is, an individual, after a few days or weeks, may become acclimatized to a certain altitude, but, if he attempts to reside at a significantly higher level, the process of acclimatization must be repeated. Henderson (38) has stated: "There are as many acclimatizations as there are altitudes at which a man can live."

Since there is a wide individual variation in adaptation to oxygen want, it is of interest to quote the conclusions reached by members of the International High Altitude Expedition to Chile (51) regarding the type of individual who is best fitted for acclimatization. Their results indicated the following: "For relatively normal men between the ages of 29 and 44, habituated at sea level, it appears that youth, a slow pulse, low normal oxygen capacity, low alveolar oxygen pressure, high alveolar carbon dioxide pressure and high alkaline reserve at sea level are favorable for acclimatization at high altitudes."

It has been mentioned already that the living organism cannot acclimate perfectly even to moderate altitudes, since, while an individual may seem to be well acclimated when at rest, as soon as he indulges in vigorous exercise he suffers from dyspnea. It has been stated (7) that all dwellers at high altitudes are persons of impaired physical and mental powers and that the acclimated man is one who is least impaired.

Acclimatization in disease.—Diseases such as those of the lung, heart, circulation, or the blood, which are often associated with

anoxia, call for a certain amount of adaptation in the body. As far as it is known, the same responses are elicited as those which take place at high altitudes. In many of these diseases the development of anoxia is slow, so that the process of adaptation comes on gradually.

Disease processes can, of course, simulate either the anoxic, the anemic, or the stagnant type of anoxia. Numerous examples could be given to illustrate each type of anoxia; but, for the present, one will suffice. A most striking instance is that reported by Goldschmidt and Light (24) in a case of patent ductus Botalli. The arterial saturation of the blood in this case was only 45 per cent, which corresponds to an oxygen tension of 25 mm. Hg (43,000 feet). The oxygen content of the arterial blood was practically normal, since there was a compensating hemoglobin increase to 32 volumes per cent capacity, or 170 per cent of the normal at sea-level. The tissues, however, were functioning at an oxygen tension of 20 mm. Hg. An ordinary individual could not have lived even for a short period under such a condition. In view of the previously discussed lower limits of oxygen tension and acclimatization, it must be pointed out that the example just mentioned is only an isolated instance. It is likely that similar adaptation exists to a considerable extent in many cases of chronic valvular heart disease, heart block, emphysema, and perhaps certain other disease processes.

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EFFECT OF ANOXIA ON THE ALIMENTARY TRACT

During the last twelve years the author and his co-workers have studied rather extensively the influence of anoxia on the alimentary tract. Recently the author has reviewed the literature in this field (49*).

In discussing the effect of anoxia on the alimentary tract the four types of anoxia will be recognized: (1) the anoxic type, (2) the anemic type, (3) the stagnant type, and (4) the histotoxic type.

THE EFFECT OF ANOXIC ANOXIA ON GASTROENTERIC MOTILITY

Swallowing movements, the esophagus, and the cardia.—No reports in the literature are available on the effect of anoxia on the swallowing movements. The swallowing mechanism is a complicated one, and there is some question as to whether the normal act of swallowing is entirely understood. The effect of anoxia on the esophagus or on the cardia has apparently not been studied either. Most of the work dealing with the effect of anoxia on the motility of the alimentary tract has been done on the stomach and pylorus.

Hunger contractions.—In 1928 Van Liere and Weaver (unpublished work) and later Van Liere and Crisler (50) studied the effect of anoxia on hunger contractions on the normal trained dog. They found a decrease in the amplitude of the hunger contractions, as registered by the balloon method. There was a distinct loss of gastric tone and a diminution in the height of the hunger contractions at a partial pressure of oxygen of 80 mm. Hg (18,000 feet). The contractions were not abolished, however, at a partial pressure of oxygen of 40 mm. Hg (36,000 feet) (see Fig. 10).

In 1935 Hellebrandt, Brogdon, and Hoopes (24) studied the effect of acute anoxia on man, using the rebreather method for inducing anoxia. They reported that the precoma type of anoxia had but slight effect on hunger contractions. In 1938 Krugly (26), working with dogs, reported that hunger contractions were inhibited at a

* See p. 183 for bibliographical references.

barometric pressure from 320 to 357 mm. Hg. His findings, for the main part, are in accord with those of Van Liere and his co-workers.

Motility of stomach containing food.—It has been shown in barbitalized dogs (11), by both the balloon and the gastrograph methods, that anoxia produces inhibition of gastric digestive motility (Fig. 11). The decrease in the amplitude of the contractions is first seen at a concentration of oxygen of about 10 per cent; at 5 per cent oxygen concentration the contractions are greatly diminished but not abol-

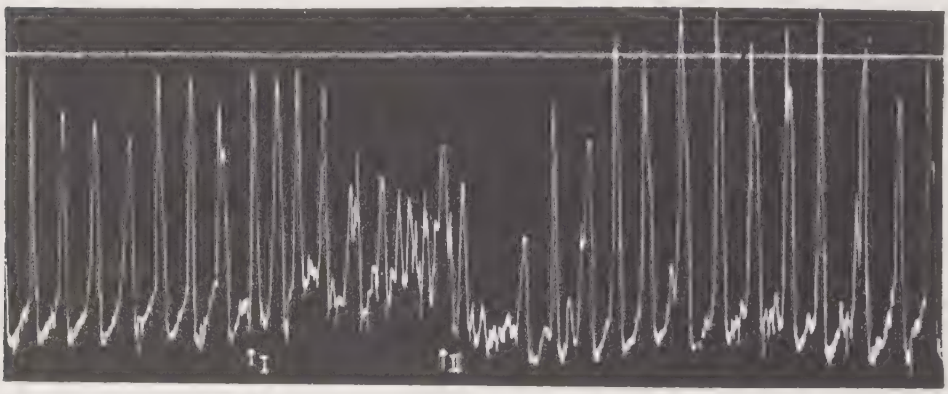


FIG. 10.—The effect of anoxia on hunger contractions in the unanesthetized dog. At *I* the oxygen percentage was changed from 20 to 5, and at *II* the animal again was allowed to breathe 20 per cent oxygen. (By permission of the *American Journal of Physiology*.)

ished. The explanation offered for the inhibition of digestive contractions produced by anoxia was a sensitization of the sympathetics by the rise in pH accompanying the initial hyperpnea and overventilation produced by anoxia.

Hellebrandt *et al.* (24) studied the effect of acute anoxia on digestive contractions in man, using the same technique as was used when hunger contractions were studied. They concluded that, while anoxia moderately depressed the motor activity of the stomach, the precoma type of anoxia had relatively little inhibitory effect upon digestive motility. Since these authors were studying the acute effects of anoxia and were using a different technique than was used on dogs, the results obtained by the two different groups of workers are not incompatible.

Effect on motility of gizzards of birds.—In 1925 Nolf (30, 31, 32) studied the effect of anoxia on the motility of the gizzards of birds. Rhythmical contractions were produced by briefly stimulating the extrinsic nerves supplying the gizzard; the contractions continued for some time after the stimulus was removed. When the animals were subjected to 8 or 10 per cent oxygen mixture, the contractions were greatly depressed; as soon as the anoxia was discontinued, the gizzards resumed their normal contractions.

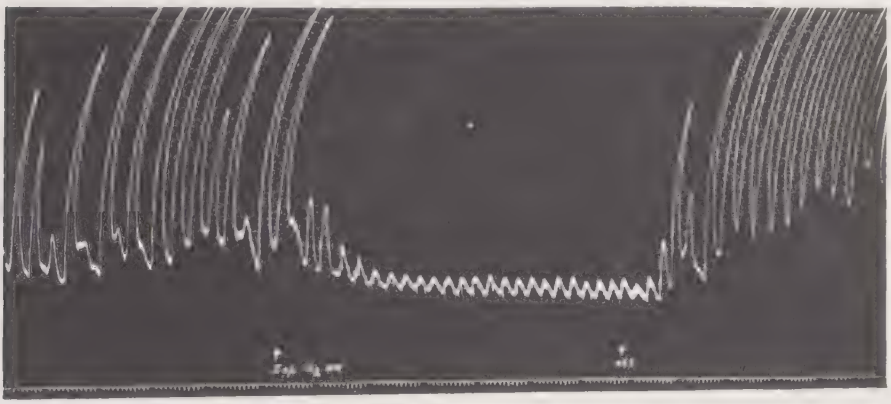


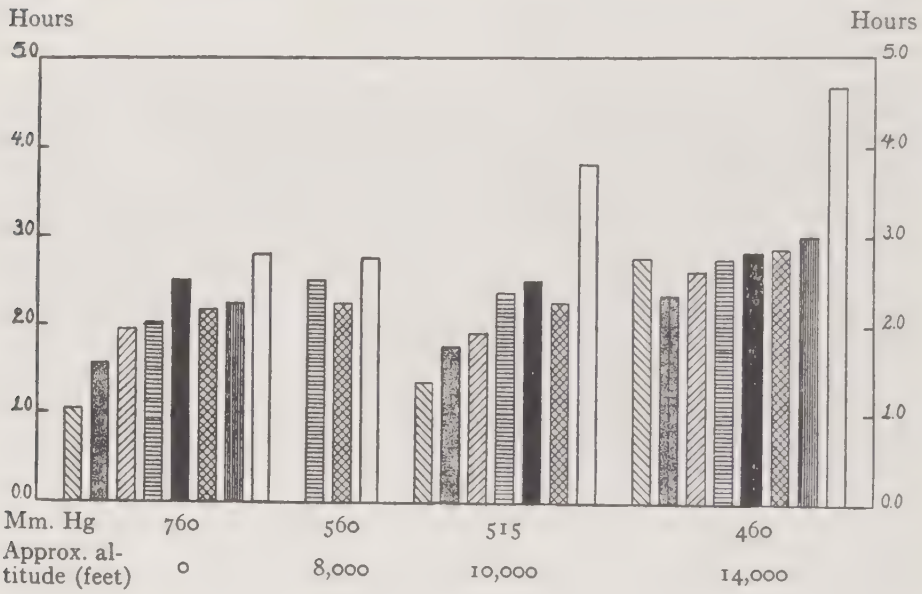
FIG. 11.—The effect of anoxia on the digestive movements of the stomach response to 5 per cent oxygen. Note decrease in amplitude and fall in tone during anoxemia and increase in both to higher than normal levels with stair-step effect during recovery. (By permission of the *American Journal of Physiology*.)

Effect on gastric emptying time.—

a) Experiments on dogs: It was shown by Van Liere *et al.*(51) in 1933 that dogs subjected to anoxia showed a delay in gastric emptying time. Since three of four dogs showed an appreciable delay in gastric emptying at a partial pressure of 117 mm. Hg (8,000 feet), the authors considered this the threshold for the normal dog. The more severe the degree of anoxia, the greater the prolongation of the emptying time. Two dogs which were subjected to a partial pressure of oxygen of 73 mm. Hg (20,000 feet) still had food in their stomachs at the end of 24 hours.

b) Experiments on man: In 1936 the author and his co-workers (55) reported work on the effect of anoxia on the gastric emptying time of eight young adult human beings. The data obtained from

the human beings correlated well with that obtained from the experiments on dogs, although the latter showed somewhat more delay in gastric emptying. The threshold for man was found to be approximately that of the dog, that is, 8,000 feet, since two of the three subjects showed a definite prolongation of gastric emptying at this altitude (Fig. 12).



Subject No.	Normal 0 Feet (Hours)	560 Mm. Hg 8,000 Feet		515 Mm. Hg 10,000 Feet		460 Mm. Hg 14,000 Feet	
		Hours	Percentage of Delay	Hours	Percentage of Delay	Hours	Percentage of Delay
1	1.03	.....	.....	1.33	29.1	2.75	166.9
2	1.55	.....	.....	1.75	12.9	2.33	50.3
3	1.94	.....	.....	1.90	— 2.0	2.60	34.0
4	2.02	2.50	23.7	2.37	17.3	2.75	35.6
5	2.50	.....	.....	2.50	0.0	2.83	13.2
6	2.17	2.25	3.6	2.25	3.6	2.87	32.5
7	2.25	.....	.....	.....	.....	3.00	33.3
8	2.80	2.75	— 1.8	3.81	36.1	4.67	66.7
Av.	2.03	.....	8.5	.....	13.9	2.98	54.1

Fig. 12.—Effect of anoxemia on the individual emptying time of the stomach in eight subjects at various pressures. In the diagram each subject is represented by the same type of shading throughout. (Diagram by permission of the American Medical Association.)

At a simulated altitude of 14,000 feet (partial pressure of oxygen of 94 mm. Hg) all the subjects showed a delay in gastric emptying. There were, however, marked individual variations; the range varied from 13.2 per cent to 166.9 per cent of the normal. Two of the individuals were subjected to a simulated altitude of 18,000 feet (partial pressure of oxygen of 80 mm. Hg). The authors concluded that in man, as in the case of the dog, the more severe the degree of anoxia, the greater the delay in gastric emptying time.

Effect of nitrous oxide anesthesia.—In discussing the effect of anoxic anoxia on gastric motility, the effect of nitrous oxide must be mentioned. In 1938 Sleeth and Van Liere (42), in making a comparative study of the effect of various anesthetic agents on gastric emptying time, found that the administration of nitrous oxide caused a delay in gastric emptying. Since in administering nitrous oxide it is necessary to use a concentration of 95 per cent, the subject actually gets only 5 per cent oxygen, an amount which, of course, produces an anoxemic state.

Mechanism of the delay in gastric emptying produced by anoxic anoxia.—Evidence has been produced (12) which indicates that the delay in gastric emptying produced by moderate degrees of anoxic anoxia is on a vagospastic-pylorospastic basis; that is, the anoxia stimulates the vagi, and this stimulation, in turn, causes some contraction of the pyloric sphincter and thus narrows the pyloric passage. This pylorospasm produced by anoxia is an important factor up to a certain threshold, beyond which further delay is caused by the oxygen want directly affecting the gastric musculature.

Another mechanism must be mentioned. It has been shown (56) in human beings that ephedrine may delay greatly gastric emptying. A number of workers (43, 70) have shown that epinephrine also produces a delay in gastric emptying. If the secretion of epinephrine is capable of being augmented by anoxia, the increased epinephrine secretion could cause a definite inhibition of gastric motility.

Effect on the pyloric sphincter.—Working with barbitalized dogs and using a pressure tonometer in the pylorus, as described by Thomas (46), it was found by Van Liere *et al.* (52) that anoxia caused a rise in the tonus of the pyloric sphincter in some animals and a fall in others. As a rule, the height of the pyloric contractions was dimin-

ished; this was especially true during severe grades of anoxia (Fig. 13). The authors attributed the variability of their results to the complexity of the control of the pylorus and to the general nature of the stimulus.

Using unanesthetized dogs with permanent gastric and duodenal fistulae and using a pressure tonometer in the pylorus, Van Liere and Thomas (61) found that anoxia caused a rise in the tone of the pyloric sphincter in fourteen out of seventeen trials. The threshold for the production for this increase of tone in the unanesthetized unacclimated dog was a partial pressure of 108 mm. Hg (10,000 feet). The effect of anoxia on the pyloric contractions in the unanesthetized dogs, however, was indeterminate. Concomitant tracings taken of the pyloric antrum showed that anoxia decreased the tone of this structure and that moderately severe grades of anoxia abolished the normal rhythmical contractions (Fig. 14).

EFFECT OF ANEMIC TYPE OF ANOXIA ON GASTRIC MOTILITY

Hunger contractions.—Carlson (8) in 1918 reported experiments performed on the effect of acute hemorrhage on hunger contractions. He found that, if dogs were bled about 30 per cent of their calculated blood volume, the tone of the stomach was increased and the hunger contractions were intensified. In less than 24 hours this augmented effect disappeared. His interpretation, for which no subsequent proof has been offered, was that the tissues, deprived of so much nutritive material, probably liberated a hormone which stimulated the hunger contractions.

Gastric motility.—Studies have been reported (60) on the effect of acute hemorrhage on gastric motility in human beings and in dogs. Four human beings from whom one-tenth of the calculated blood volume had been withdrawn showed, on the average, a prolongation of gastric emptying time of 41 per cent. In no case was it less than 25 per cent. In three of the men there was still a delay of from 15 to 20 per cent 24 hours after the hemorrhage. At the end of 48 hours the stomach had apparently regained its normal activity.

Two dogs from which one-tenth of their blood volume was withdrawn also showed a noticeable delay in gastric emptying, thus confirming the results obtained in man.

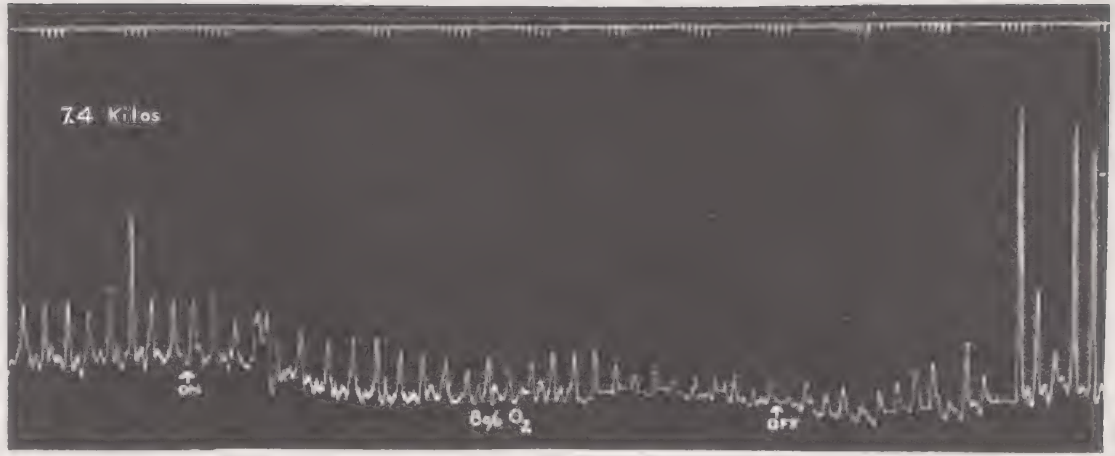


FIG. 13.—Effect of anoxemia on the pyloric sphincter. (*1*) Eight per cent oxygen; anoxemia produced a fall of tone and a diminution in the height of the pyloric contractions. (By permission of the *American Journal of Physiology*.)

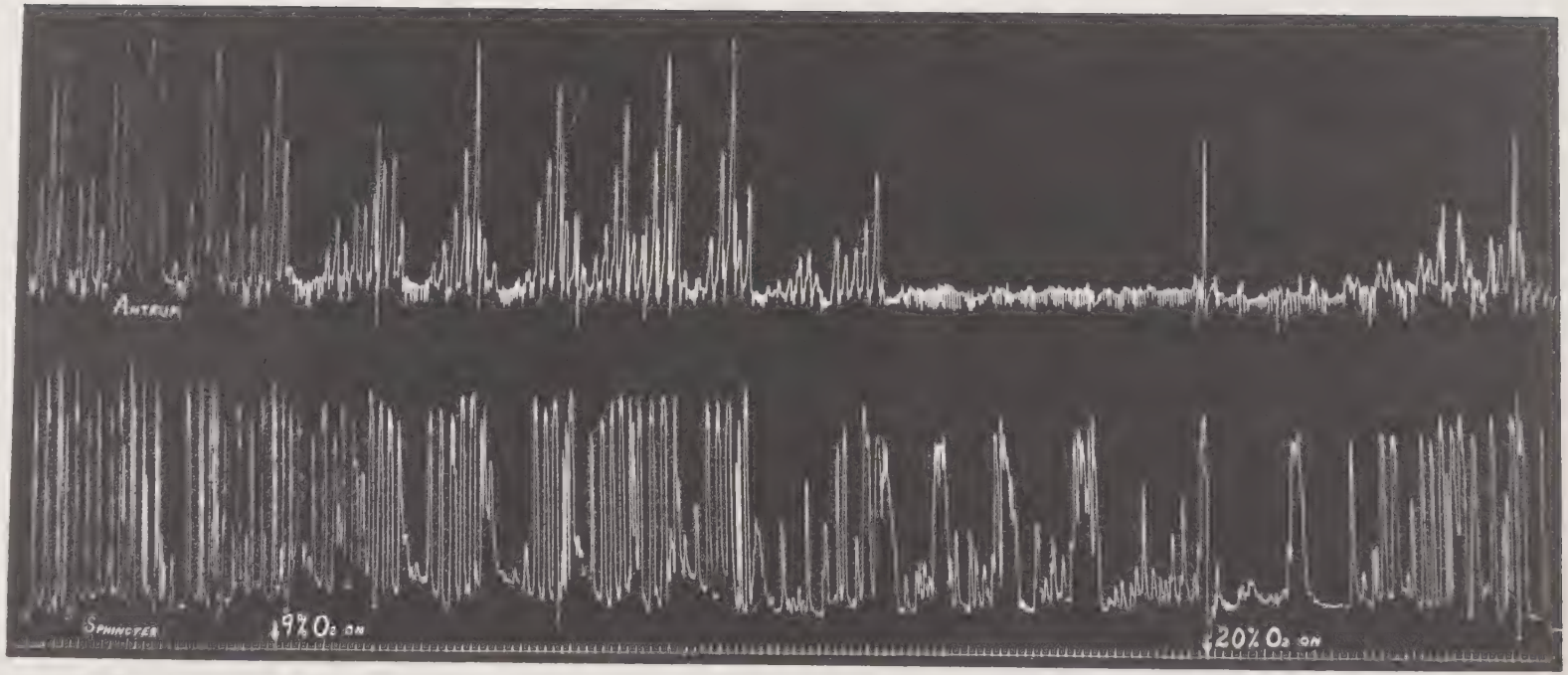


Fig. 14.—Effect of anoxemia on the pyloric sphincter and the antrum in unanesthetized dogs. (By permission of *American Journal of Digestive Diseases.*)

Using the balloon method for observing gastric motility, Curtis and Hamilton (13) reported studies made on patients afflicted with pernicious anemia. An intense gastric motility was observed, which persisted during liver therapy and continued even after marked clinical improvement was noticed in the patient. Although the mechanism producing the augmentation was not clear, the authors suggested that it might have been produced by the associated anacidity or possibly by stimulation of the gastric neuromuscular apparatus by pathological changes in the stomach. In a case of hypoplastic anemia these authors, using the same method of registering gastric motility, also reported continuous motility of frequent contractions of high amplitude.

Carbon monoxide.—Carbon monoxide produces an anemic type of anoxia since it unites with the hemoglobin transporting the normal amount of oxygen. There is evidence, however, that it also may act as a histotoxic agent. Working with rats, Peterson *et al.* (36) reported that chronic monoxide asphyxia inhibited gastrointestinal peristalses.

EFFECT OF STAGNANT ANOXIA ON GASTRIC MOTILITY

Cardiac failure, impaired venous return, or shock may produce this type of anoxia. It is known clinically that certain cardiac diseases may produce nausea and vomiting as well as minor gastric disorders; in fact, any condition which impairs the circulation may produce these symptoms.

No quantitative data or any carefully controlled work on the effect of stagnant type of anoxia on gastric emptying could be found in the literature. It would be difficult to obtain trustworthy data on clinical patients, since, in order for the work to be well controlled, it would be necessary to know what the normal gastric emptying time of the patient had been before the stagnant type of anoxia had developed. Besides this almost insuperable difficulty, others would present themselves, such as the relative physical inactivity of the patient, the psychic factor in cardiac disease, and the like. Since any or all of these factors could influence gastric emptying, it would be necessary, indeed, to evaluate very carefully any results obtained.

EFFECT OF HISTOTOXIC ANOXIA ON GASTRIC MOTILITY

In discussing this type of anoxia, the cyanides should be mentioned first of all, since they exert the greatest depression on cellular oxidation. At present the cyanides are not widely used in medicine. They are present, however, in the syrup of wild cherry, and this preparation is often used in compounding prescriptions.

No reports of the effect of the cyanides or of any other agent unequivocally producing histotoxic anoxia on the gastroenteric tract in the intact animal could be found in the literature. Some work has been done, however, on isolated intestinal strips. In 1918 Alvarez (2) reported that the more highly active portions of the isolated strips of small intestine are inhibited more by cyanides than are less active strips.

While it is not in the province of this monograph to make fine distinctions as to which agents may affect cellular respiration, it may be stated with reasonable safety that the following well-known preparations may produce a histotoxic type of anoxia: the barbiturates, bromides, urethane, chloral, ether, chloroform, vinethene, ethylene, cyclopropane, and, to a lesser extent, carbon monoxide. Nitrous oxide produces the anoxic type of anoxia, as previously explained. While carbon monoxide produces mainly an anemic type of anoxia, it is believed that it, too, is capable of interfering with cellular respiration. It must also, then, be classified as an agent producing a histotoxic type of anoxia.

Opinion varies as to the degree of histotoxic anoxia produced by the inhalation anesthetics during surgical anesthesia. An experienced anesthetist, Dr. R. M. Waters (65), has insisted that general anesthetics, even when surgical anesthesia is produced, should not, if properly given, produce anoxia. All general anesthetic agents in some measure, however, produce respiratory depression; so, unless the anesthesia is carefully given, anoxia may be produced. It is particularly difficult to avoid anoxic anoxia when nitrous oxide is the sole anesthetic agent.

Sleeth and Van Liere (42) in 1938 made a comparative study of common inhalation anesthetic on gastric motility in dogs. Surgical anesthesia (third plane) was induced rapidly and maintained for 15 minutes. The animals ate the test meal as soon as they recovered

from the anesthesia. Fluoroscopic examination showed that all the anesthetic agents used prolonged gastric emptying: chloroform by 64 per cent; ethylene, cyclopropane, and divinyl oxide each about 7 per cent. Nitrous oxide probably produces anoxic anoxia, as previously explained; and this probably explains the longer delay with this agent than with the other gases.

Using Macht's technique, Emerson (16) found that surgical anesthesia with ether inhibits the motility of the small intestine of rats for the period of its duration. Normal activity of the intestine was regained by the second hour after anesthesia was terminated.

Some authors have interpreted these results as being due to sympathetic stimulation; but, if later work shows that these anesthetic agents exert a histotoxic effect in surgical anesthesia, their action could be explained on this basis.

What histotoxic effects fixed narcotics may produce are probably outweighed by their effects on smooth muscle or on its innervation.

EFFECT OF ANOXIA ON THE MOVEMENTS OF THE SMALL INTESTINE AND COLON

Small intestine.—That fulminating anoxia can stimulate intestinal peristalsis may be easily demonstrated. If a guinea pig is struck a blow on the head, and the abdomen opened at once, the small intestines in many instances may be seen to undergo a very active peristalsis. This initial stimulation, presumably produced, for the main part, by the acute anoxia, is but transitory in nature and is soon followed by a paralysis of the intestine.

Schnor (39) in 1934 reported studies on the effect of anoxia on intestinal peristalses. He inserted an oval cellophane window in the abdominal wall of rabbits and found that anoxia or an increase in carbon dioxide concentration in the blood caused violent contraction of the arteries of the intestines and an immediate cessation of all intestinal movement.

The work of Emerson (16) on the effect of ether surgical anesthesia on the motility of the small intestine has been mentioned under the discussion on histotoxic anoxia.

The influence of carbon monoxide was mentioned briefly when the effect of anemic anoxia was discussed on gastric motility. Peterson

et al. (36), using a modification of Macht's technique, in studying the effect of carbon monoxide on gastrointestinal peristalsis in rats, found that, if the blood is saturated from 70 to 80 per cent with carbon monoxide, gastrointestinal peristalses were inhibited 33 per cent. What they termed "the egestion time," that is, the time required for the first appearance of fecal pellets following the test meal, was prolonged 22 per cent.

Since, so far as it is known, the innervation of the small intestine is similar to that of the stomach, it is likely that anoxia would affect both structures similarly; the difference, if any, would be one of degree. The results obtained, then, by the various workers on the effect of anoxia on the motility of the small intestine are not unexpected.

More quantitative work is needed, however, on the effect of various degrees of anoxia on the motility of the small intestine in both man and animals. Such studies might throw some light on the problem of paralytic ileus as well as on other intestinal disturbances. Work on this problem presents some difficulties, since it is hard to carry out these studies and maintain the intestine in a normal physiologic state. Owing to the mass of the small intestine, it is difficult to obtain accurate quantitative data, especially in animals, from fluoroscopic studies. The introduction of fistulae may interfere with normal intestinal behavior and even with the normal health of the animal. In such a study, if several different methods could be used and if similar results were obtained by two or more methods, the data could probably be considered trustworthy.

The colon.—No work has been reported in the literature on the effect of anoxia on colon motility. It would be unsafe to predict what effects anoxia would have on its movements, since it has a different innervation from that of either the stomach or the small intestine, and, further, different parts of the colon have a different innervation. The blood supply of the colon is believed by some (17) to be less rich in oxygen than the upper part of the gastroenteric tract. If this is true, the colon may be relatively resistant to anoxia. More studies are needed on this particular point.

Intestinal gases at high altitudes.—Gases which have accumulated in the alimentary tract expand as the barometric pressure falls. At an altitude of 18,000 feet, which corresponds approximately to ½ at-

mosphere of pressure, these gases will expand to double their volume (1). It was suggested by Zuntz and his co-workers (71) in 1906 that the expansion of these gases was the explanation for the reduced vital capacity experienced at high altitudes. It was shown later, however, that this view was untenable (regarding vital capacity see p. 115). The pressure of these gases against the abdominal wall and diaphragm may cause unpleasant sensations. Diets rich in carbohydrate foods, which ferment and form gas, would have a tendency to aggravate this condition.

Armstrong (5) has called attention to the action of these gases in the alimentary tract during aircraft ascents. According to this author, in an ascent of 200–300 feet per minute the expansion of the gases will produce a moderate amount of abdominal distention when an altitude of about 12,000–16,000 feet is reached, and belching may then occur, as well as an urge to pass flatus. If the ascent is rapid, such as 1,000 feet or more per minute, however, the gas tends to become localized in pockets in the intestines and does not pass off. As a result of this, abdominal cramps of varying severity may appear at altitudes between 15,000 and 20,000 feet; and at extreme altitudes, such as 30,000 or 35,000 feet, they practically always occur and may persist for several hours. Ordinarily, descent will relieve the distress, but in severe cases the cramps may last as long as 24 hours.

It is thought that in the normal, healthy individual the distention of gases has no deleterious effect either on the heart or on the respiration. Since it is known, however, that distention of abdominal viscera may reflexly affect other organs, it is not unlikely that the distention of gases in the gastroenteric tract produced by high altitudes might be a distinct hazard to individuals in poor health.

Summary of the effect of anoxia on gastrointestinal motility.—It has been seen that it is necessary to subject both man and animals to what may be regarded as a moderately severe grade of anoxia before the movements of the alimentary tract are significantly affected. Since this is true, it may be inferred that the nausea and vomiting produced by high altitudes are not due to a direct effect on the stomach. Some people suffer from mountain sickness at altitudes as low as 7,000 feet. No pronounced change at this altitude has been observed in gastric motility either in man or in the dog.

Carlson has pointed out that normal hunger contractions may produce a feeling of faintness and nausea in certain pathological conditions. It may be that mountain sickness can cause such a condition in some people.

Aviators insist that moderate degrees of anoxia are often accompanied by hunger sensations. It is also known that airplane passengers frequently request that substantial meals be served. All these people doubtless confuse hunger with appetite. It is not improbable that in men certain altitudes may cause some stimulation of hunger contractions, although carefully controlled work on dogs gave no indication of this; as a matter of fact, in general, the effect of anoxia on gastrointestinal movements is one of depression.

It must be emphasized that the effect of anoxia on gastric emptying shows a good deal of individual variation both in man and in animals. At an altitude of 12,000 feet, at which transcontinental planes fly, individuals who are particularly sensitive to oxygen want show a noticeable retardation in gastric emptying, whereas those who are less susceptible are but slightly affected.

It must be recognized that a moderate diminution of gastric motility is of no clinical importance. Before any significant impairment in the behavior of the stomach is noted, anoxia doubtless causes cerebral manifestations and cardiac dysfunction. Compared to the central nervous system, the gastroenteric tract is relatively resistant to anoxia.

ANOXIA AND PERMEABILITY

In the brief discussion allotted to anoxia and permeability in this monograph, no attempt will be made to discuss in detail the effect of anoxia on cell permeability. The reader is referred to the volume by Gellhorn and Regnier (19) and to the reviews of Wilbrandt (68), Collander (10), Toerell (47), Hober (25), Osterhout (35), and others. Most of these reviews mention, in one way or another, the effect of oxygen want on the permeability of the cell.

The work of Hamburger (22) on the intestine, Bainbridge (6) on the permeability of the visceral capillaries, Starr (44) on the kidney, Landis (27) on the capillary, Magee and Macleod (28) on the intestine, and Van Liere and his co-workers (49) on the gastrointestinal

tract indicate how important a role anoxia may play in physiologic functions.

Hamburger (22), as early as 1896, performed experiments on the passage of salt through dead membranes (see p. 176, regarding salt absorption); Bainbridge (6) in 1906, in explaining some of the factors concerning the flow of post-mortem lymph, suggested that lack of oxygen increased the permeability of visceral capillaries. The glomerular filtrate in a kidney with normal circulation is protein free, as shown by Wearn and Richards (66). However, Starr (44) in 1926 showed that, if the blood flow is stopped, or even a reduction made in its rate of flow, a transient albuminuria not accompanied by any visible pathological change is produced.

Landis (27) has made interesting observations on anoxia and capillary permeability. In 1928 he reported the effects on capillary permeability of oxygen, high tensions of carbon dioxide, and increased hydrogen-ion concentration in single capillaries of the frog mesentery. He produced oxygen lack by compressing the mesenteric artery and vein and found that, after a 3-minute period, the permeability was so increased that the fluid in the capillary filtered through the walls at approximately four times its normal rate. Not only did the fluid pass through the capillary wall, but the protein did as well, so that the effective osmotic pressure of the plasma was reduced to one-half its normal value. The capillary wall recovered its impermeability as soon as the circulation was allowed to return.

The capillary permeability to fluid was slightly increased when the mesentery was exposed to Ringer's solution completely saturated with carbon dioxide, but it remained normally permeable to protein; one-half saturation of carbon dioxide had no effect.

Within physiological limits an increase in hydrogen-ion concentration produced practically no change in capillary permeability, which proved that it was the oxygen lack, and not the change of pH, which produced the change in tissue permeability. In 1929 Magee and Macleod (28) reported that sugars and electrolytes passed through devitalized segments of intestine more rapidly than they did through normal intestinal segments.

Anoxia and permeability of stomach to water.—In order to study this problem, Sleeth and Van Liere in 1937 (41) studied the effect

of severe degrees of anoxia on the permeability of gastric epithelium to water. A partial pressure of 53 mm. of Hg was the most severe degree of anoxia used in these studies. No appreciable influence on the absorption of water by the stomach was noticed even though the animals were exposed to the anoxia for an hour or more. It was concluded that anoxia does not affect the permeability of the stomach to water.

ANOXIA AND ABSORPTION

In their studies on the effect of anoxia on the alimentary tract the author and his colleagues did considerable work on absorption under anoxic conditions. The reader is referred to the recent review (49), previously mentioned, on the effect of anoxia on the alimentary tract.

Method of studying the problem.—In reviewing the early literature dealing with anoxia and absorption, practically no mention is made of the degree of anoxia used; and various methods are employed, most of which are unphysiologic, such as shutting off the blood supply, producing injury to the epithelium by the application of corrosive chemical agents, and the like. These methods leave the tissues in an unphysiologic state: if the blood supply is completely shut off, a complete and fulminating anoxia is produced, which may lead to irreparable injury; corrosive agents destroy the tissues so that they become a dead membrane rather than a normal, semipermeable one. It is obvious that only limited conclusions can be drawn from experiments employing these methods.

The author and his co-workers, in their studies on absorption, made an effort to avoid the criticisms just outlined and employed a procedure as follows: Matched pairs of dogs (or cats) which had had no food 48 hours previous to the experiments were used. Intravenous sodium barbital (220 mg. per kilogram) was used for an anesthetic. One animal served as a control, and the other was subjected to anoxia. An isotonic solution of either sodium chloride or glucose, heated to body temperature, was used to wash out the debris from the small intestine. The entire small intestine, with the exception of the duodenum, was used for a loop. The loops of the two dogs were made of the same length by actual measurement.

The substance to be studied was brought to body temperature be-

fore it was placed in the intestine. Substances were left in long enough so that, on the average, at least 50 per cent was absorbed. Undue distention of the intestine was avoided. The contents of the loop at the end of a given time were removed, measured, and quantitatively analyzed for the substance in question. In most of the studies reported various degrees of anoxia were used, ranging from a partial pressure of oxygen of 117 mm. Hg (8,000 feet) to that of 53 mm. Hg (28,000 feet).

Absorption of water.—Studies on the effect of various degrees of anoxia on absorption of water from the small intestine have been reported (53). The absorption of water was unaffected by anoxia until a partial pressure of 80 mm. Hg (18,000 feet) was reached, at which partial pressure of oxygen considerably more water was absorbed by the anoxic dogs than by the controls. The results statistically analyzed were quite significant. At lower partial pressures of oxygen (63 and 53 mm. Hg) the anoxic dogs still showed an increase in water absorption, but not as much as they did from the small intestine of the mammal at 80 mm. Hg. No adequate explanation can be given for this; but, in passing, it is of interest that this occurred at what Barcroft has termed a "critical level" of anoxia.

It has been shown (57) that ephedrine, administered either orally or intravenously, has no appreciable effect on the intestinal absorption of water. This is of interest since it is believed by some workers that there is an increase of epinephrine secretion during anoxia. Added to this should be mentioned that it has been shown by Rudolf and Graham (38) that ephedrine produces vasoconstriction of the intestines.

In anemic anoxia it has been found (58) that less distilled water was absorbed from the small intestine of dogs which had suffered a hemorrhage of 3.2 per cent of their body weight. This decrease in absorption of water may be due to the fall of blood protein after hemorrhage. It has been shown by Wells (67) that the absorbing force is proportional to the protein concentration of the blood.

In discussing the effects of anoxia on the absorption of water from the small intestine it must be remembered that water, and especially distilled water, is not a normal constituent of the small intestine. Recently it has been shown by Dennis (15) that water is distinctly

injurious to epithelium of the lower ileum, as shown by the interference with the impermeability of this membrane to the sulphate radical and with the ability of the epithelium to do osmotic work.

The studies made on the effect of various degrees of anoxia on the absorption of water, however, are still of interest, since whatever damage the water did to the epithelium of the intestine was presumably the same at various levels of anoxia, thus controlling this factor.

Absorption of sodium chloride.—In 1896 Hamburger (22) reported that absorption of salt solution in the intestine of dogs, dead from 1 to 24 hours, proceeded in the same manner as in living dogs. Magee and Macleod (28) in 1929 found that the walls of segments of intestine after devitalization became more permeable to solutions of sugar and electrolytes. These men obviously were working with dead membranes.

Working with barbitalized dogs and using various degrees of anoxia, Van Liere and Sleeth (59) found that absorption of isotonic sodium chloride solution was somewhat decreased even by mild degrees of anoxia (partial pressure of oxygen of 117 mm. Hg). The absorption of fluid and the actual sodium chloride absorption ran parallel. It was concluded that oxygen aids in the absorption of physiological sodium chloride solution from the small intestine.

The author and his co-workers (57) found that ephedrine, administered either orally or intravenously, had no effect on the intestinal absorption of isotonic sodium chloride solution. It will be recalled that ephedrine produces a vasoconstriction of the blood vessels in the splanchnic area.

In anemic anoxia (58) it has been observed that dogs which had been bled 3.2 per cent of their body weight absorbed more physiological salt solution from the small intestine than did the control dogs. The results obtained with anemic anoxia were in contrast to those obtained by anoxic anoxia. This probably may be explained on the basis that severe hemorrhage produces a depletion of chlorides throughout the tissues of the body, so that when chlorides are placed in the intestine following a hemorrhage they pass into the blood stream more rapidly because of the higher diffusion gradient.

Absorption of sodium chloride in the presence of the sulphate radical.—Although the mechanism is not understood, it is known that the chloride ion is absorbed more readily from the intestine in the presence of the sulphate radical (21). Van Liere and Vaughan (62) studied the effect of various degrees of anoxic anoxia on the absorption of a solution consisting of equal parts of isotonic sodium chloride and isotonic sodium sulphate solution from the small intestine of bar-

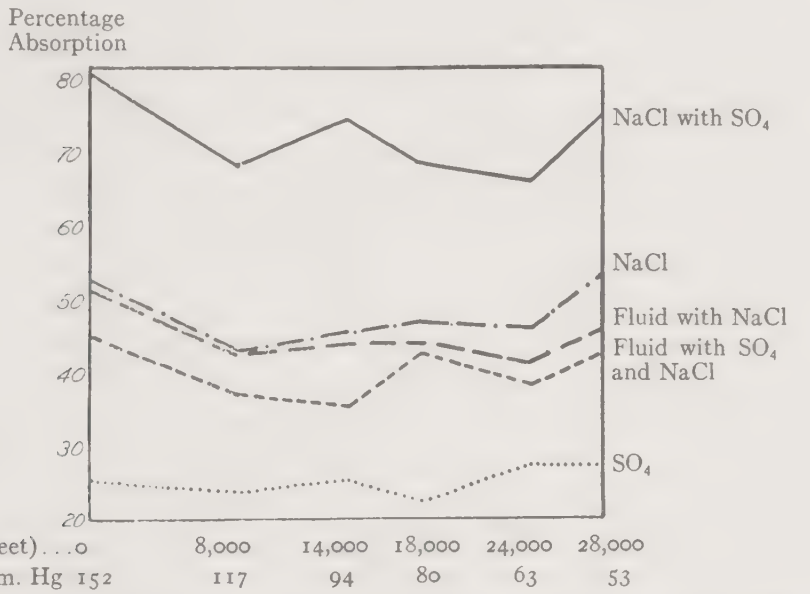


FIG. 15.—Effect of various degrees of anoxia on absorption of chloride ion in presence of a sulphate radical. (By permission of the *American Journal of Physiology*.)

bitalized dogs. Although anoxia depressed somewhat the absorption of the fluid and the sodium chloride, it did not prevent the facilitation of the absorption of the chloride ion due to the presence of the sulphate radical. This study also showed that anoxia had no effect on the absorption of sodium sulphate (Fig. 15).

Absorption of the sulphate radical.—The absorption of isotonic magnesium sulphate is not affected by ranges of anoxia compatible with life in barbitalized animals (33). The absorption of sodium sulphate, as just mentioned in the preceding paragraph, is likewise unaffected by anoxia. These studies indicate that the permeability of the intestine to the sulphate radical is unaltered even by severe de-

grees of anoxia. This is of distinct clinical importance, since magnesium sulphate especially is given, in many instances, to patients with cardiac disorders which are often associated with anoxic states. This salt has a powerful depressant action on the central nervous system and, if absorbed in excess, might produce death.

Glucose absorption.—Gellhorn and Northup (18) have shown that, while circulatory factors can affect glucose absorption, the effects are so inconstant that in a large series they can be ignored. It has been found (unpublished work) that even moderately severe degrees of anoxic anoxia do not affect the absorption of glucose from the small intestine. When severe degrees of anoxia (partial pressure of oxygen of 53 mm. Hg) are used, however, glucose absorption is increased, but the increase is not statistically significant.

Ephedrine, which is known to produce vasoconstriction of the splanchnic region, either given orally or intravenously, does not influence the absorption of glucose from the small intestine (57).

It has further been shown (58) that anemic anoxia, produced by bleeding dogs 3.2 per cent of their body weight, also has no effect on the absorption of glucose.

Apparently glucose absorption involves a phosphorylization process rather than an oxidative one (64, 69), and this probably explains the reason for even moderately severe degrees of anoxia not affecting its absorption. Since very severe degrees of anoxia (partial pressure of oxygen of 53 mm. Hg or less) markedly increase the absorption of glucose, it is likely that these severe degrees of anoxia increase the intestinal permeability to glucose.

Absorption of glucosides.—Work done on barbitalized cats shows that even a severe degree of anoxia (partial pressure of oxygen of 53 mm. Hg) has no effect on the absorption of digitalis per se or on the fluid menstruum (54). This is of practical interest, since digitalis is often administered to cardiac patients who are markedly cyanosed and obviously suffering from considerable anoxia.

Absorption of amino acids.—The absorption of glycine (unpublished work) is unaffected by moderately severe degrees of anoxia (partial pressure of oxygen of 80–63 mm. Hg), but at more severe degrees of anoxia it is significantly decreased.

Summary of the effect of anoxia on absorption.—In evaluating the studies made on the effect of anoxia on absorption, it may be concluded safely that ranges of anoxia compatible with life would not, as far as absorption is concerned, interfere with the proper nourishment of the body. Whether allergic manifestations, however, would be produced by the increased permeability often brought about by severe anoxia remains to be shown. It is possible that certain split-protein products might pass through the intestinal epithelium during severe degrees of anoxia and produce unphysiologic effects. The problem suggests a field of research which, in so far as the author is aware, remains untouched.

Probably the main value of the studies of anoxia and absorption is the light they throw on the fundamental mechanisms of absorption processes and especially of the role of physiological oxidations. It has been postulated that the mechanism of glucose absorption is a phosphorylization process rather than an oxidative one. Studies in glucose absorption and anoxia lend support to this theory, since even moderately severe anoxia does not decrease its absorption. Studies made with other substances have shown how anoxia may affect the permeability of the intestinal epithelium.

These studies, however, are not solely of academic interest; some clinical importance may be attached to some of them. It is of interest, for example, that digitalis is not appreciably influenced by anoxia. It also is important that the absorption of the sulphate radical is not increased by anoxia, since it is so widely used in conditions which are associated with anoxia. As a point of fact, negative findings are at times as important as are positive ones. Much more work is needed on the effect of anoxia on absorption; thus far only a few simple substances have been studied.

THE EFFECT OF ANOXIA ON GASTRIC AND INTESTINAL SECRETION

Relatively little work has been reported on the effect of anoxia on secretion. As far as the author is aware, the only reports in the literature are those which deal with the effect of anoxia on the stomach, intestine, and kidney.

Effect of anoxic anoxia on the gastric secretion.—In 1911 Bayeux (7), working with dogs at an altitude of 14,000 feet, found that while

the total acid was not affected the volume of gastric juice was diminished. Delrue in 1934 (14) reported that when his dogs were transported from his laboratory to an altitude of 8,000 feet the gastric juice showed a decrease in pH and total acid. In 1935 Hellebrandt, Brogdon, and Hoopes (24) subjected human beings to short periods of anoxia which was produced by a rebreathing apparatus. They reported that anoxic anoxia of the precoma type caused no appreciable decrease in gastric acidity.

In 1936 Sleeth and Van Liere (40) subjected barbitalized dogs, which had had water placed in their stomachs, to various degrees of anoxia. It was only after a partial pressure of oxygen of 53 mm. Hg (28,000 feet) was reached that there was a definite diminution in the acidity and chlorides in the gastric contents.

In 1939 Pickett and the author (37) studied the effect of various degrees of anoxia on gastric secretion of a series of dogs with Pavlov pouches and on a series with Heidenhain pouches. In this connection it must be remembered that a stomach pouch made according to the method of Pavlov has a normal blood and nerve supply; the Heidenhain pouch, however, is an isolated pouch, and, while it has an adequate blood supply, it presumably has no vagal nerve supply.

The most severe degree of anoxia used was that corresponding to a partial pressure of oxygen of 63 mm. Hg (24,000 feet). At a partial pressure of oxygen of 117 mm. Hg (8,000 feet) most of the animals showed some diminution in the secretion of gastric juice; this was still more noticeable at a partial pressure of oxygen of 94 mm. Hg (14,000 feet). The decrease in gastric secretion, however, was not statistically significant until a partial pressure of 80 mm. Hg was reached. The authors felt that the threshold for the average dog probably lay between 14,000 and 18,000 feet. The more severe the degree of anoxia, the greater was the decrease of gastric juice. Anoxia, however, affected the volume of the gastric juice of the Heidenhain group more than it did the Pavlov group (Fig. 16).

Other differences were noted in the two groups of animals in their responses to anoxia. In the Pavlov group the pH of the gastric secretion did not change until a partial pressure of 63 mm. Hg was reached, whereas the Heidenhain group was affected at 80 mm. Hg.

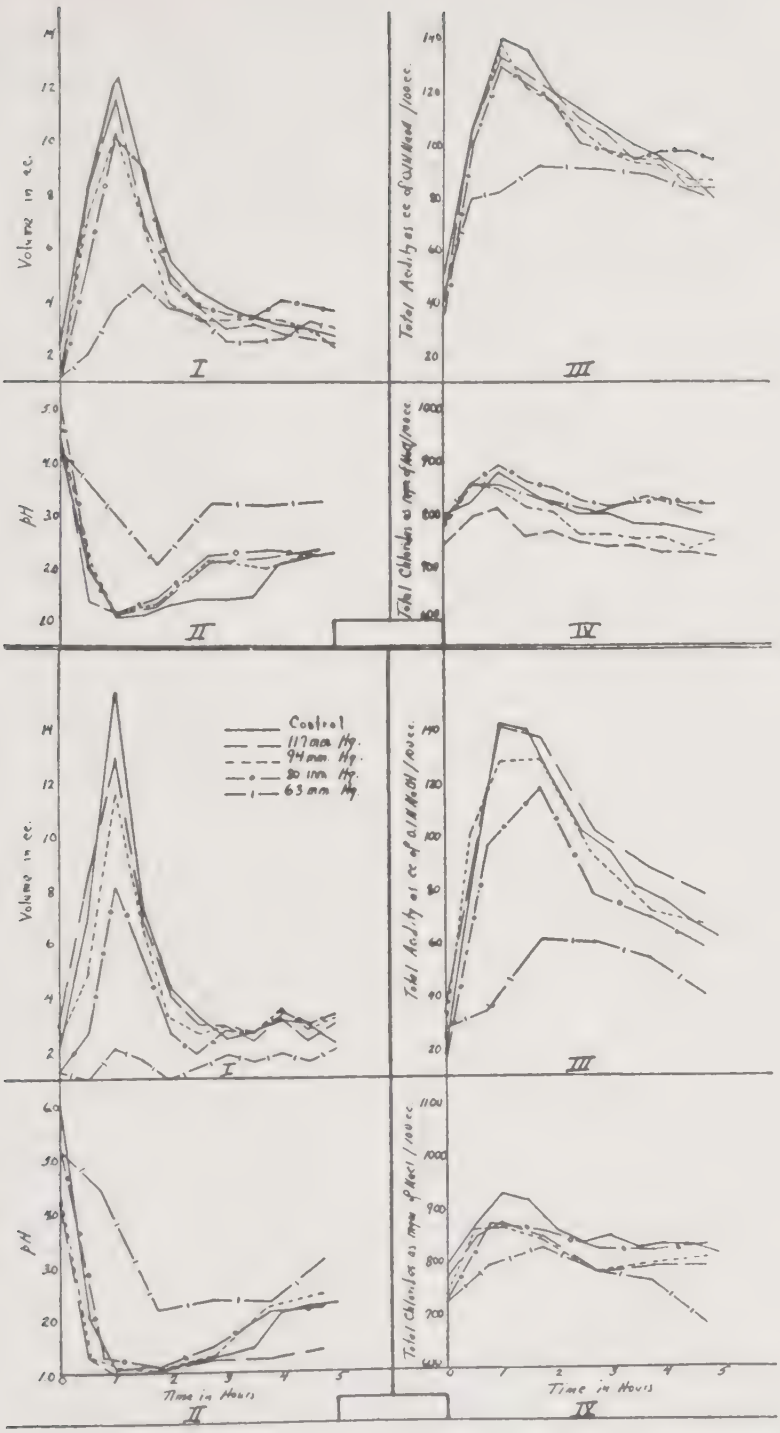


FIG. 16.—The effect of anoxia on gastric secretion. In the upper half of the figure (*I–IV*) are the results obtained with Pavlov pouch dogs, while in the lower half (*I–IV*) are those obtained with Heidenhain pouch dogs. (By permission of the *American Journal of Physiology*.)

The data obtained for total acids were just the reverse of those obtained for pH. The total chlorides in the gastric secretion of the Pavlov group were not affected by the ranges of anoxia used, but in the Heidenhain group the total chlorides were decreased significantly at an oxygen partial pressure of 94 mm. Hg.

The conclusions drawn were that the Heidenhain group was affected by less severe degrees of anoxia than the Pavlov group but that all animals showed a decrease in gastric-juice secretion if subjected to effective degrees of anoxia.

Effect on basal secretion.—It has been shown (63) that anoxic anoxia, within ranges compatible with consciousness in unacclimatized dogs, has no effect on the chlorines, acids, or pH of the basal secretion of Pavlov pouch dogs. Moderate ranges of anoxia do not affect the volume of basal secretion as much as the secretion provoked by food; severe anoxia, however, depresses the basal secretion as it does the secretion called forth by food.

Effect of anemic anoxia on gastric secretion.—A number of interesting observations have been made on the relation between the hemoglobin content of the blood and gastric acidity. Alvarez and Vanzant (3) in 1936 reported a study on a large number of human beings concerning this relationship. It was found that the incidence of achlorhydria rose rapidly and that the mean gastric acidity fell off sharply when the hemoglobin fell below 12 gm., or 72 per cent. They concluded from their work that loss of blood in both animals and man can lower temporarily gastric acidity.

Hartfall and Witts (23), studying cases of idiopathic microcytic anemia, found in a series of one hundred and thirty-seven cases that 80 per cent gave evidence of achlorhydria; they did not feel, however, that the low acidity was secondary to the anemia. In subjects afflicted with pernicious anemia Goldhamer (20) found a direct relation between the red cell count and the amount of gastric juice secreted within a given time.

In 1936 Apperly and Cary (4) showed experimentally that, when the red cell count of the blood fell below a certain critical level, free acid disappeared from the stomach.

When the effects of anemic anoxia and anoxic anoxia are compared, it appears that anemic anoxia has more profound effect on

depressing gastric juice than has the anoxic type. The loss of chlorides during hemorrhage may be one reason for this.

Anoxia on intestinal secretion.—In 1939 Northup and Van Liere (34) studied the effect of various degrees of anoxia on intestinal secretion in barbitalized dogs. In order to secure sufficient secretion with which to work, the small intestine was made to secrete by injecting intravenously a peptone extract prepared according to the method described by Nasset and Pierce (29). It was only when a partial pressure of oxygen of 53 mm. Hg (28,000 feet) was reached that a slight depression of secretion occurred; and this decrease, moreover, was not statistically significant even though fifteen animals were used. The authors concluded that the intestine had a low energy requirement.

Summary of the effect of anoxia on secretion.—While experimental work shows that anoxic anoxia is capable of diminishing gastric secretion, it can be seen that, for the main part, the gastric glands are relatively resistant to oxygen want. It is only during severe degrees of anoxia that the secretion is appreciably decreased. Anemic anoxia, as previously mentioned, apparently affects gastric secretion more than does the anoxic type. This is of interest; and since pernicious anemia is associated with achlorhydria, more research could be done profitably in this particular field. The secretion of the intestine seems to be so resistant to oxygen want that, for practical purposes, the effect of anoxia on its secretion is largely of academic interest.

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ANOXIA AND THE SECRETION OF URINE

ANOXIC ANOXIA

The effect of anoxic anoxia on kidney secretion in the intact animal has been studied by only a few workers. In 1933 Adolph (1*) reported work on the effect of oxygen want on the frog's kidney. He found that during total absence of oxygen, urine formation ceased entirely; 4 per cent oxygen, however, prevented this reaction; and when 3 per cent oxygen was administered, some urine still was formed. It was observed that the lack of oxygen constricted the renal arterioles, so that the blood flow in all the glomeruli was stopped. Denervation of the kidney did not change the response of these vessels to oxygen want. Adolph concluded that the effect of asphyxia on the frog's kidney had the same effect as ligating the renal arteries.

Working with barbitalized dogs, Van Liere *et al.* (9) showed that breathing oxygen tensions from 5 to 12 per cent caused a diminution in the secretion of urine in forty-five out of fifty experiments on twelve dogs. Although there was considerable variation, the threshold was thought to be approximately 12 per cent oxygen. In some instances anoxia produced a polyuria, and occasionally at the cessation of the period of anoxia there appeared a marked polyuria, which resembled a supernormal phase.

Toth (6) in 1937 reported that in anesthetized dogs the breathing of low oxygen tensions (10 per cent for $1\frac{1}{4}$–$2\frac{1}{2}$ hours) generally resulted in oliguria but occasionally in polyuria. His results, in the main, coincided with those reported by Van Liere and his co-workers. Toth also found that the rates of urea and chloride excretion vary directly with the excretion of water. The animals which responded with an oliguria showed, in the majority of the experiments, a temporary proteinuria and a glycosuria.

In a later paper Toth (7) reported a study on the effects of epinephrine on urine secretion in anesthetized dogs. If the intravenous infusions were given rapidly, oliguria resulted; but if given slowly,

* See p. 189 for bibliographical references.

polyuria was caused. Both the effects found in anoxic anoxia, therefore, could be produced by epinephrine administration. It was also found that the urinary urea concentration decreased after epinephrine infusions. During the periods of oliguria which resulted from the rapid infusion of epinephrine a proteinuria usually occurred; but when a polyuria was produced by a slow infusion, the urinary protein, as a rule, was unaffected.

In a subsequent paper Toth (8) found that the elimination of adrenal secretion from the circulatory system (produced by tying off the adrenal glands) did not prevent the oliguria that usually resulted in normal kidneys when they suffered from anoxia. When the kidney was denervated, however, under the same experimental conditions, the rate of urine flow did not decrease but accorded with that expected from the changes that occur in the general systemic blood pressure.

Mode of action of anoxic anoxia on urine secretion.—It was suggested by Van Liere *et al.* (9) that the oliguria produced by anoxia might be due to the action of epinephrine. From the work of Toth, however, it appears that the oliguria cannot so be explained, since the effect persists even though the secretion of the adrenal glands was not permitted to enter the circulation. It was also mentioned by the first-named workers that the oliguria might be explained on a nervous basis. The fact that the urine rate did not decrease during anoxia in the dog after the kidneys were denervated suggests that this explanation might be the true one. Since, however, anoxic anoxia at times may produce an oliguria and at other times a polyuria, it is quite clear that more work is needed to establish clearly the mode of action of anoxia on the kidney.

Clinical observations.—Armstrong and his associates (2) subjected individuals daily to a simulated altitude of 12,000 feet in a low-pressure chamber; one group was maintained at this level for 4 hours and another for 7 hours. It was found that, on the average, the amount of urine increased to 100 per cent over normal and on certain days 300 per cent over normal. There was some decrease in specific gravity, but not in proportion to the increase in volume, which indicated an increased elimination of solids as well as fluids from the body.

In 1937 McFarland and Edwards (4) studied the urine output in

men making transpacific flights. These men flew at altitudes from 8,000 to 12,000 feet (average, 9,460 feet) and were in the air 122.5 hours. The volume of urine secreted in the two observers was unaffected by anoxia, but there was a tendency toward polyuria in the airmen who were responsible for the handling of the ship. As the flight progressed, however, this polyuria diminished.

In the experiments reported by Armstrong and his associates and by McFarland and Edwards the individuals upon whom the experiments were performed were at altitudes not over 12,000 feet. This corresponds approximately to 13.23 per cent of oxygen. It must be recalled that Van Liere and his co-workers found that 12 per cent oxygen was about the threshold for the average barbitalized dog. It would be of interest to measure the secretion of urine in human beings at greater heights.

It is difficult to explain the results reported by Armstrong and his associates. It is true that both Van Liere and his co-workers and Toth found polyuria, but this finding was the exception rather than the rule, and it was not noticed at any particular altitude, as was the one mentioned by Armstrong. The polyuria reported by McFarland and Edwards in the officers of the ship who were about to make a transpacific flight can be explained by the increased nervous tension. This was recognized by the authors, who stated that the results they obtained from the airmen were like those commonly observed in athletes previous to competition.

STAGNANT AND ANEMIC ANOXIA

It has been demonstrated, by Wearn and Richards (10) in 1924, that the glomerular filtrate in a kidney with a normal circulation is protein free. It was shown by Starr (5) in 1926, however, that if the blood flow was stopped or even a moderate reduction in its flow produced, a transient albuminuria was caused which was not accompanied by any visible microscopical pathological change.

HISTOTOXIC ANOXIA

Beck, Kempton, and Richards (3) in 1938 studied the action of cyanide (and oxygen lack) on glomerular function in perfused frog's kidney. They found that glomerular vessels are usually constricted by cyanide (and also by oxygen lack), so that oliguria often resulted.

Cyanide increases the permeability of the glomeruli, but the amount of flow will depend upon the amount of constriction of the vessel. It was further found that dilute solutions of cyanide increased the permeability of the tubules to water.

Résumé of anoxia on kidney secretion.—Clinically, it is known that heart failure, with diminished arterial supply and venous congestion (stagnant anoxia) of the kidney, increases the permeability of the glomerular epithelium, so that albumin or even blood may appear in the urine.

The experimental findings in both man and animals indicate that the kidney is capable, however, of withstanding a marked degree of anoxic anoxia. For practical purposes the effect of anoxic anoxia on the kidneys may be ignored, since grave disturbances would be produced in the central nervous system before the kidneys would be affected appreciably.

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EFFECT OF ANOXIA ON THE ENDOCRINE GLANDS

With the exception of the adrenals and the gonads, relatively little work has been reported on the effect of anoxia on the endocrine glands.

THE EFFECT ON THE ADRENALS

Although a number of workers (5*, 6, 7, 8, 12, 15, 16, 29) have reported that anoxia stimulates the adrenals, leading to a liberation of epinephrine, there has been considerable controversy regarding this matter. Cannon and his co-workers (5, 8) have maintained for many years that there was clear-cut evidence that anoxia, among other factors, causes an increased secretion of epinephrine. On the other hand, Stewart and Rogoff and their associates (30) have presented, from time to time, certain conflicting evidence. It is not possible in the space permitted here to give in detail the evidence presented at various times by the above-mentioned workers. The reader is referred to the original work of these investigators.

The English worker Kellaway (16, 17, 18) in 1919 presented some evidence that anoxia can stimulate the adrenals to increase their output of epinephrine. Schulze (29) also concluded that anoxia stimulated the adrenals. Both these workers found an increase in blood sugar following exposure to anoxia. It has been maintained by Rogoff (25, 26) that the adrenals are not necessary for the rise in blood pressure in cerebral anemia.

Grollman (14) has stated that the type of anoxia is important; for example, anoxia produced by carbon monoxide stimulates epinephrine secretion, while anoxic anoxia may or may not do so. If this view is correct, it explains the discordant results obtained by various workers.

It suffices to say here that there are still two schools of thought regarding the question of whether or not anoxic anoxia actually calls forth an increased secretion of epinephrine. The author feels, however, since sympathetic effects often occur during anoxic anoxia,

* See p. 194 for bibliographical references.

that there is good grounds for believing that the adrenals definitely may be stimulated.

Exhaustion of the adrenals by anoxia.—

a) The adrenal cortex: In 1937 Giragossintz and Sundstroem (13), working with rats under conditions of very low levels of atmospheric pressure for an extended period of time, believed that the functional alterations observed were identical with those seen in cortico-adrenal insufficiency in adrenalectomized animals. When cortical hormone was administered to these animals, the effects were ameliorated. These workers further observed that histological sections of the adrenals showed that prolonged anoxia produced cellular necrosis and hemorrhage. It was felt that structural damage was due to the overwhelming demand on the glands made by anoxia and that this eventually resulted in exhaustion.

A year later Armstrong and Heim (2), working with rabbits and subjecting them for 4 hours daily to a simulated altitude of 18,000 feet (379 mm. Hg barometric pressure), made findings similar to those reported by the workers previously mentioned. They first noted a hypertrophy of the whole adrenal gland and later observed degenerative changes in the cortex. The hypertrophy was quite marked; in one group of animals exposed daily for a period of 5 months the average weight of the adrenal glands was 400 per cent greater than those of the control group. Armstrong suggested the possibility that the fatigue seen in both acute and chronic altitude sickness might be related to adrenal insufficiency or exhaustion.

b) The adrenal medulla: In the same year (1938) Emerson and Van Liere (11) also presented some evidence that anoxia may exhaust the adrenals. They subjected cats for 3 hours to a simulated altitude of 28,000 feet (246 mm. Hg barometric pressure) and found a 40 per cent decrease in the adrenin content of the adrenal glands, as determined by an adaptation of the Moodey (22) colorimetric method. It is true, of course, that this work did not distinguish between a decreased rate of formation of epinephrine or an exhaustion of its stores.

In summary, it may be said, then, that there is considerable evidence that anoxic anoxia may exhaust the adrenal glands; but whether this bears any relation to altitude sickness remains to be proved.

THE EFFECT OF ANOXIA ON THE GONADS

It has been known for several hundred years that inhabitants at high altitudes, including man and animals, lose their fertility and may not be able to bear young. Monge (20) has studied the early records of the Spaniards, relative to their experiences in the Andes. It was related by Father Cobo that, while the natives were quite prolific, the Spaniards showed a greatly reduced birth rate and that miscarriages and stillbirths were common. There are records stating that so many animals died at birth that the capital of Peru in 1535 was transferred from Juuja (10,000 feet) to Lima, which is approximately at sea-level.

Monge also called attention to the observations made by Father Calancha (9, 21), who wrote that the Spanish conquerors, who worked the mines at Potosí, Bolivia, which lie at an altitude of 14,000 feet and more, had no offspring until 58 years after the city was founded.

Not only does anoxic anoxia produce a loss of fertility, but the anoxia produced by carbon monoxide poisoning may likewise do so. There is considerable evidence that carbon monoxide may produce impotence. In 1912 McCombs (19) reported that men surviving acute carbon monoxide poisoning are sometimes impotent, and Rossiter (27) in 1928 called attention to the fact that men exposed to chronic carbon monoxide poisoning in the steel industry not infrequently complain of a loss of sexual desire. Williams (34) has written that carbon monoxide poisoning may cause death and expulsion of the fetus in human beings. It has been reported in the literature, also, that repeated exposures to carbon monoxide caused a tendency for rabbits and mice to abort (3).

Experimental evidence has been offered to show that carbon monoxide may cause loss of fertility and may also produce changes in the gonads in male animals. Campbell (4) in 1935 exposed white mice to increasing concentrations of pure carbon monoxide (24 parts per 10,000 were reached on the forty-sixth day) and found that after prolonged exposure the mice lost their fertility, although there was but little disturbance in their growth.

In the same year Williams and Smith (33) exposed rats to 1.43 per cent illuminating gas daily for a certain length of time. Fertility

was decidedly reduced, and the testes weighed only one-third to one-half of those of a control group. After 60 days' treatment no living spermatozoa were found by the hanging-drop method. The females which were mated with normal males were less fertile than the control animals. On histologic examination the ovaries were not abnormal, although they were smaller.

Patterson, Smith, and Pickett (23) in 1938, working with rats, reported that the combined testis and epididymis weight in rats was reduced about one-half after fifty or more 1-hour exposures to illuminating gas, that the number of spermatozoa was greatly decreased, and that the motility of the few viable sperm was impaired.

There appears, then, to be abundant proof that carbon monoxide poisoning can produce changes in the male gonads. The apparent sensitivity of the gonadal cells to carbon monoxide suggests, however, that carbon monoxide may exert a histotoxic action which may be more important than its anemic action. This phase of the problem should be studied further.

THE EFFECT OF ANOXIA ON THE THYROID

It was pointed out by Streuli (31) in 1918 that thyroidectomized animals are considerably less susceptible to oxygen want than are normal animals. While statistical data probably are needed to establish this point indisputably, it is reasonable to suppose that Streuli's observations are correct; inasmuch as metabolism is lowered after thyroidectomy, the animal requires less oxygen. In this connection it is of interest to recall that Haldane pointed out long ago that small animals, which are known to have a high metabolic rate, are more sensitive to carbon monoxide than are large animals.

A number of observations have been made on the effect of carbon monoxide poisoning on the thyroid. It has been suggested that carbon monoxide asphyxia is capable of producing hyperthyroidism. Raab (24) has reported the case of a young girl who developed hyperthyroidism following exposure to carbon monoxide. Drinker (10) has criticized this report, however, on the grounds of insufficient evidence.

Schulze (28) in 1936 subjected white mice 10 minutes daily to carbon monoxide (5 parts in 10,000), a concentration which was

capable of causing symptoms and even death in some animals. After 12–16 days' treatment certain changes in the staining of the thyroid occurred, consisting of a heavy basophilic staining of the colloid material. These animals also showed an increase in basal metabolism.

It has been shown definitely that the effect of carbon monoxide on metabolism depends upon the severity and length of exposure. Schulze (28) has shown that brief periods of asphyxia with long periods of recovery may increase the metabolism, and Walthers (32) has shown that with slow and severe poisoning depression of metabolism occurs.

It is apparent that more work is needed on the effect of anoxia on the thyroid. It is believed that there are many factors which may cause the development of hyperthyroidism; reports, therefore, that exposure to mild concentrations of carbon monoxide for brief periods is capable of producing hyperthyroidism must be accepted with a good deal of hesitation.

THE EFFECT OF ANOXIA ON THE HYPOPHYSIS

Patterson, Smith, and Pickett (23) in 1938 subjected a group of rats to carbon monoxide poisoning (a gas-air mixture was used which contained 0.34 per cent carbon monoxide) for an hour a day for periods from 50 to 131 days. The hypophyses upon histological section showed vacuolated and enlarged basophils; the histological picture resembled that produced by castration described by Addison (1) in 1917.

The gonadotropic potency of the hypophyses was measured by noting the response of the ovaries and uteri of immature female rats. It was observed that the gonadotropic hormone was increased. It appears, therefore, that the effect of carbon monoxide poisoning on the hypophyses is secondary to a deleterious effect on the gonads. As far as the author is aware, no work has been reported on the effect of chronic anoxic anoxia on the hypophysis.

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METABOLISM AND ANOXIA

OXIDATIVE METABOLISM

It is now generally believed that gaseous metabolism is independent of variations in barometric pressures. Gaseous metabolism during anoxic conditions has been studied by three different methods: (1) by the use of a low-pressure chamber, (2) by balloon ascensions, and (3) by mountain ascents.

Zuntz (27*), as early as 1897, using a low-pressure chamber and working at a barometric pressure of 448 mm. Hg (14,000 feet), found that the exchange of carbon dioxide and oxygen was unchanged from the normal both at rest and during muscular exercise.

A number of observations on metabolism have been made on Monte Rosa. One of the early reports was that of Durig and Zuntz (7) in 1904. Working at an altitude of 15,000 feet (430 mm. Hg) during a sojourn of $2\frac{1}{2}$ weeks, they found that the resting metabolism increased as much as 15 per cent above that of sea-level. It was not due to cold, since the readings were taken while the subject was in a warm bed. At an altitude of 10,500 feet negative results were reported. Durig (6) in 1909, working with six subjects on Monte Rosa, found increases in the amount of oxygen absorbed ranging between 9.9 and 45.5 per cent. In the same year Fuchs and Deimler (8), also working on Monte Rosa, found an increase in carbon dioxide production and oxygen absorption above that of sea-level, and it was proportionately greater during standing than while reclining at rest.

Studies in metabolism were also reported by members of the Anglo-American Expedition to Pike's Peak in 1911 (4). The respiratory exchange of Douglas was only slightly greater on Pike's Peak than at sea-level. The gaseous metabolism during muscular exercise was found unchanged with altitude.

In 1915 Hasselbalch and Lindhard (14) found no change in the exchange of carbon dioxide and oxygen in a low-pressure chamber at

* See p. 199 for bibliographical references.

atmospheric pressures ranging from 589 mm. Hg (7,000 feet) to 448 mm. Hg (14,000 feet). Each man spent a number of days in the chamber.

Sundstroem (23) in 1919 found no appreciable change in gaseous metabolism between that at high altitudes and that at sea-level. Viali (25) in the same year, at the Mosso Scientific Institute on Monte Rosa, reported work with two subjects. One showed an increase in metabolism the first 5 days, which returned to normal during the succeeding 5 days. The other subject showed no initial rise, as did the first, but showed and maintained an increment of about 11 per cent oxygen. The respiratory quotient was increased at high altitude.

In 1923 Schneider (21) reported some studies in respiratory exchange, during a sojourn on Pike's Peak, in men sitting at rest and during a moderate amount of exercise. At rest two of the three men showed no change in the gaseous metabolism above the normal established at sea-level; the third man showed a slight rise for the first 48 hours and then returned to normal. During moderate exercise there was some increase in the rate of metabolism for the first few days, but within 1–3 days six of the seven men showed no exchange above that of sea-level.

In 1927 Kestner and Schadow (16), reporting work done on the Jungfraujoch, concluded that the slight increase in the basal metabolism rate found was attributable to the increased activity of the respiratory muscles.

Finally, Monge (18), who has had a great deal of experience working with people in normal and in ill-health who reside at high altitudes, states that the basal metabolism of normal persons living at high altitude is normal. He accepts the findings of Hurtado (15).

If, as is customary, a rather wide latitude is allowed in metabolism readings (plus or minus 15 being within normal range) the results obtained by the various workers indicate that even moderately high altitudes have no marked effect on metabolism either in the resting state or during moderate exercise. Probably more work is needed, however, on metabolic studies at extreme altitudes, since Ogata (19) reported that rabbits showed a decrease in oxygen consumption during severe anoxia.

The effect of carbon monoxide on metabolism.—Conflicting results have been reported in the literature on the effect of carbon monoxide on metabolism. It has been reported by some (11, 26) that carbon monoxide produces a decrease in metabolic rate in animals, while others (20, 22) have reported the opposite results. Killick (17) has pointed out that, when the experimental findings are summed up, it seems that if the animals are exposed to low concentrations of carbon monoxide and if the anoxia develops slowly the metabolic rate is slowed; but, on the other hand, if the anoxia is severe and rapid the metabolic rate may actually rise as a result of increased activity of the respiratory muscles (10). She further points out that it must be recognized that in experiments (20, 22) in which the animals were subjected to repeated severe poisonings the ductless glands were affected, so that the metabolism was increased.

Only a few observations have been reported on the effect of carbon monoxide on the metabolism in the human being. Beck (1) in 1936 found that the metabolic rate was significantly reduced in just over half of his patients who had been exposed repeatedly to carbon monoxide. Drinker (5) in 1938 made the observation that frequently in acute carbon monoxide poisoning a marked fall in body temperature occurs, presumably because of depressed metabolism.

NITROGEN METABOLISM

It has been shown by a number of workers (3, 12, 13, 14, 23) that anoxic anoxia produces a decrease in the excretion of ammonia. It is thought that this decrease is a response, as previously mentioned, to the alkalosis of hyperpnea (p. 123). While Brunquist *et al.* (2) in 1924 found that there was a terminal increase in the rate of total nitrogen excretion, as well as of ammonia and creatine, in little pigs which had been subjected to fatal reductions of oxygen tensions, it is believed that in nonfatal degrees of anoxia these effects do not appear.

Carbon monoxide anoxia and metabolism.—An increase in urinary excretion of total nitrogen and of ammonia in carbon monoxide poisoning has been reported by several workers (9, 24). In 1928 Tscherkess and Melnikova (24) reported that in various animals both uri-

nary nitrogen and inorganic phosphorus were increased during and after periods of severe carbon monoxide anoxia. These workers claimed that this indicated increased destruction of protein and a raised metabolic rate; they did not, however, report any other method of estimating the rate of metabolism.

Since it is generally believed that anoxia produced by carbon monoxide has practically the same effect as does anoxic anoxia, it is difficult to explain the results reported by the above-mentioned workers. It would appear that before any conclusion is drawn their work should be repeated and careful studies made on the metabolic rate.

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ANOXIA AND HEAT REGULATION

It was reported in 1910 by Bayeux (2*) that rabbits which had been transported to a height of 4,350 meters (14,272 feet) showed a decrease in body temperature. Several years previously he had made observations on himself and his wife on the summit of Mount Blanc and had found a reduction in the axillary temperature. Bayeux regarded the hypothermia observed at high altitudes as being due not to fatigue or cold but to an actual decrease of the physiological oxidations of the body.

Behague *et al.* (3) in 1927 placed rabbits in a chamber from which air could be withdrawn and reported that reduction in the air pressure was paralleled by fall of temperature in the animals. They concluded that the hypothermia was produced by the reduced oxidation resulting from the oxygen deficiency.

In 1935 Hamon *et al.* (7) also found that the temperature of the body falls with decreasing atmospheric pressure. These authors showed that the decrease in body temperature resulting from oxygen want is associated with a decrease in oxygen consumption and that a small animal like a mouse was more affected than a larger animal with a relatively smaller body surface area.

Gellhorn and Janus (6) in 1936 proved that it was the oxygen tension in the inhaled air which determined the effect of anoxia on body temperature; and Gellhorn (5), working further on this problem, came to the same conclusion as did Hamon *et al.* (7), that the loss in body temperature associated with anoxia is greatest and develops most rapidly in animals with a relatively large surface area, such as the mouse. He found that mice died at elevated temperatures when exposed to an oxygen pressure which could be tolerated at ordinary room temperature. When 3 per cent carbon dioxide was added to the inhaled air, the fall in body temperature was increased. He believed this indicated that the fall in body temperature is not regulated exclusively by the oxygenation of the tissues but that the specific in-

* See p. 202 for bibliographical references.

fluence of carbon dioxide on the circulatory system plays an important part.

Drinker (4) has called attention to the marked fall in body temperature often found in man in acute carbon monoxide poisoning. This fall in body temperature accompanies the depression of metabolism.

Armstrong and his collaborators (1) have studied the effect of anoxia on body temperature in subjects who were exposed daily to a simulated altitude of 12,000 feet. One group was allowed to remain at this altitude for 4 hours, and another group for a 7-hour period. During the control periods the subjects showed an average morning temperature $\frac{1}{4}°$ below the afternoon reading. After exposure to anoxia the 4-hour group showed a difference of $\frac{1}{2}°$ of temperature between morning and afternoon; and the 7-hour group, a difference of $1\frac{1}{2}°$.

These authors concluded that the body temperature remained practically normal immediately following moderate degrees of anoxia but that within the succeeding 24 hours it dropped below normal, to an extent depending upon the duration and possibly the severity of the exposure. While they could offer no explanation for this loss in body temperature, they did suggest that the anoxia might have a direct effect on the heat-regulating mechanism of the body or that it might act indirectly as a consequence of the resultant fatigue.

Obviously, more research is needed in the field of temperature regulation and anoxia.

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ANOXIA AND NUTRITION

Reference has already been made to the fact that beyond a certain critical altitude animals will not eat (2*) (see "Acclimatization," p. 151). While working on the production of cardiac hypertrophy by anoxic anoxia, the author (9) noticed that the animals, although they received the choicest food, did not eat well and that practically all of them lost weight. In 1931 Lintzel (7) reported that rats which had been kept at a barometric pressure of 280 mm. Hg (28,000 feet) lost 20 per cent of their weight within 3 weeks.

Observations made on men at high altitudes corroborate the observations made on experimental animals. It is unnecessary to say that the newcomer to high altitudes who suffers from mountain sickness for the first few days does not eat substantial meals. What interests us here are those people who make longer sojourns at high regions.

Barcroft (1), the leader of the expedition to the Peruvian Andes in 1921–22, called attention to the fact that the appetite of the members was often capricious and irregular. In fact, he stated that one of the most notable physiologic features was the loss of weight which the men suffered; all members of the party were affected. One individual who suffered the greatest loss declined in weight from 155 to 131 pounds in 27 days.

Hingston (4), medical officer for the 1924 Mount Everest Expedition, observed that at severe altitudes (beyond 21,000 feet) the appetite became impaired and that most of the men lost their taste for solid foods but still enjoyed sweets, fruits, and soups. The consensus was that at extreme altitudes sweets were the most palatable and meats the least. These men were, of course, well acclimated. The Mount Everest climbers who lived from 6 to 7 weeks above 20,000 feet lost from 30 to 50 pounds (3).

In nine members of the International High Altitude Expedition to Chile there was a mean loss of weight of 18 pounds (8). Keys (6) has stated that the appetite may be capricious at high altitudes but

* See p. 205 for bibliographical references.

that sweet foods, such as chocolate and jams, are often relished. It was of interest that those who had the greatest difficulty in becoming acclimated showed the greatest loss of weight.

Dwellers at high altitudes.—It has been observed by a number of investigators that people who make their home in high altitudes are not obese, as a rule. Hurtado (5) reported that in comparison with similar racial stock at sea-level the Andean native children are significantly underweight. Barcroft (1) has stated that he was informed that newcomers to the high plateau region of Peru all lost weight; if the subjects remained at high altitude, they subsequently regained some of it, although the former sea-level weight was seldom reached.

The fact that people who live at high altitudes are not obese cannot be explained alone on the basis of the effect of oxygen want on the gastrointestinal tract. It has been shown (see chapter on anoxia and alimentary tract [p. 159]) that the gastroenteric tract is relatively resistant to anoxia; this is true not only for motility but for secretion and absorption as well. There are several likely reasons to account for the initial loss of weight of the newcomer to high altitudes, as well as for the subnormal weight of the native dweller of high plateau regions. As has been mentioned, the appetite is not normal, and there are often minor gastrointestinal disturbances, such as a diarrhea. In many instances it is difficult for these men to procure sound, refreshing sleep; this would tend to prevent them from gaining weight. Exertion at high altitudes, even in the well-acclimated individual, leads to dyspnea, although it is known that metabolism during moderate exercise is unchanged at high altitudes; so presumably the wear and tear of the body machinery is no greater.

There may be more subtle reasons which as yet are not understood thoroughly. It may be that the reduction in cellular oxidation brought about by the oxygen want may be responsible in part for the inability of these people to maintain their normal weight. At any rate, it is known that the entire body often shows an impairment of function at high altitudes, and it may be this general impairment which is responsible for the subnormal weight of people in high altitudes.

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EFFECT OF ANOXIA ON WATER DISTRIBUTION IN THE BODY

It was shown by Smith (1*) in 1928 that relatively small differences in barometric pressure may have a definite effect on water distribution in the body. He reported water retention in dogs and rats after they had been exposed for a period of 12–48 hours to a barometric pressure varying from 734 mm. Hg (1,000 feet) to 662 mm. Hg (4,000 feet). The water had a tendency to increase in the periphery and presumably, by stimulating the nerve endings in the skin, produced restlessness in the animals. He explained the restlessness of animals before a storm as being due to a redistribution of water from the interior to the periphery, caused by the changing barometric pressure; it was suggested, further, that human beings might be similarly affected.

Lawless (unpublished work), working in the author's laboratory, has made a study of the effect of more severe degrees of anoxia on the water content of various tissues in the white rat. The tissues studied were: the cerebrum, kidney, liver, striated muscles, skin, and adrenals. The animals were exposed to anoxia for $3\frac{1}{2}$ hours. Barometric pressures of 556, 382, and 254 mm. Hg, corresponding to altitudes of 8,000, 18,000, and 28,000 feet, were used.

At each level of anoxia a significant reduction in body weight occurred. At a barometric pressure of 556 mm. Hg there was no significant change in the water content of any of the tissues examined, but at 382 mm. Hg there was a significant reduction in percentage of water in striated muscle and in the skin. At a barometric pressure of 254 mm. Hg the skin still showed a significant reduction in the water content, but that of the striated muscle was normal. The adrenals, on the other hand, showed a significant increase in percentage of water at this severe degree of anoxia.

It is difficult to interpret the changes in water content which occurred in some of the tissues during moderate and severe degrees of anoxia. Because the animals lost weight at all the levels of anoxia, it

* See p. 207 for bibliographical references.

would be expected that the skin would show a loss in water content, since it presumably is the main water depot of the body.

The increased water content of the adrenals at high grades of anoxia may be associated with increased activity of the adrenals, but no proof has been offered for this supposition.

The decrease in percentage of water of striated muscle at a barometric pressure of 382 mm. Hg with a return to the normal at 254 mm. Hg pressure is, indeed, hard to explain. The animals probably were more active at 18,000 feet, and this might have influenced the water content of the striated muscle, although this is merely a supposition. The changes which occurred in the muscle probably were associated with certain chemical changes in the body produced by the anoxia. More work is needed on the entire problem of fluid distribution during anoxic states.

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EFFECT OF ANOXIA ON THE NERVOUS SYSTEM

Of all the tissues in the body, nervous tissue is the least capable of withstanding oxygen want. Whereas cartilage tissue, for example, may withstand total deprivation of oxygen for several hours without suffering any apparent deleterious effects, nervous tissue can withstand deprivation of oxygen for only a few minutes. Since nervous tissue is so sensitive to oxygen want, it is obvious that in discussing the effect of anoxia on the intact organism its effect on the central nervous system is of paramount importance.

EFFECT OF ANOXIA ON THE BLOOD SUPPLY TO THE BRAIN

The literature on cerebral circulation has been reviewed by Wolff (174*); in this review is included a discussion of the effect of decreased oxygen supply and also the influence of carbon dioxide on the brain circulation. The reader is referred to this review for details concerning this important subject.

It has been shown by Schmidt (148) and by Schmidt and Pierson (149) that oxygen deficiency produces vasodilatation and an increased volume of blood flow to the medulla oblongata and the hypothalamus. It has also been shown by several workers (34, 102, 175) that anoxia produces a dilatation of the pial vessels. It is of interest, however, that inhalation of carbon dioxide produces a more marked vasodilatation of the vessels which supply the brain than does oxygen want (174). In asphyxia, presumably, there is, therefore, a greater amount of dilatation of the cerebral vessels than during anoxic anoxia.

Although considerable evidence has been offered that anoxia produces an increased blood supply to the brain, it is believed that, in spite of this, the diminished oxygen tension during anoxic anoxia produces a deficient oxygen supply to the brain. It is thought, at least, that during anoxic anoxia the brain is one of the first organs to be affected.

* See p. 249 for bibliographical references.

HISTOLOGICAL STUDIES ON THE STRUCTURAL CHANGES IN THE NERVOUS SYSTEM PRODUCED BY ANOXIA

1. *Studies made following anemic anoxia.*—Anemic anoxia of the brain was produced experimentally by occlusion of the arterial blood supply as early as 1836 by Astley Cooper (35) and by others since then (69, 85, 134). Also, resuscitation of the brain by perfusion of the isolated head has been performed by several groups of workers (79, 96, 134). Histological studies, too, of nervous tissue have been made on the differential effects of anoxia following the production of anemia.

Gomez and Pike (72) in 1909, working with cats, reported histological changes in nerve cells brought about by total anemia of the central nervous system. They found that the order of susceptibility of the cells of the central nervous system to oxygen want, as shown by histological studies, was as follows: small pyramidal cells, Purkinje cells, cells of the medulla oblongata, cells of retina, cells of cervical cord, cells in lumbar cord, and sympathetic ganglion cells.

Gildea and Cobb (69) in 1930 studied the pathological effects of cerebral anemia; they observed nonspecific cortical lesions, such as focal areas of necrosis and swollen and shrunken ganglion cells. The most pronounced effect was noted in the cells of lamina III and IV of the cortex.

Weinberger *et al.* (71) in 1940, working with cats, produced temporary anemia by occluding the pulmonary artery. At the end of 3 minutes and 10 seconds permanent and severe pathological changes were found in the cerebral cortex. Longer periods of anemic anoxia produced lesions in the Purkinje cells of the cerebellum and nerve cells in the basal ganglia.

It is evident, as would be expected, that anemic anoxia produces grave organic changes in the cells of the central nervous system within a relatively short time. However, it has been emphasized by Sugar and Gerard (159) that, while the damages which follow sudden anemia are primarily due to anoxia, there are other important contributing factors; those which they mention are: hypoglycemia, hypercapnia, and the increased extracellular potassium.

A number of authors (86, 87, 130) have described lesions in the brain following carbon monoxide poisoning. It will be recalled that

carbon monoxide produces an anemic type of anoxia. Following death from carbon monoxide, the brain is said to be hyperemic and edematous, and it usually shows punctate hemorrhages. Not only has necrosis of nerve fibers in the brain been observed, but necrosis in the peripheral nerves as well (90, 147). In 1934 Yant *et al.* (176) made extensive investigations of the histological changes produced in the central nervous system of dogs following the administration of carbon monoxide; they reported the presence of various pronounced lesions. The interesting question has been raised by Thorner and Lewy (165) whether the cerebral changes in carbon monoxide poisoning are typical of anoxia or are caused in part by other factors.

2. *Studies made following anoxic anoxia.*—Recently Thorner and Lewy (165) reported experiments performed on guinea pigs and cats which had been subjected to complete anoxia by being placed in an environment of pure nitrogen for various periods of time. These workers reported that exposures to sublethal periods of pure anoxia produced vascular and degenerative changes in the central nervous system. It was pointed out that some of these changes were irreversible and became summated in animals repeatedly subjected to anoxia.

Reports have been made in the literature (72, 107) that, following fatal cases of nitrous oxide–oxygen anesthesia, lesions of the brain, especially in the cortex and basal ganglia, have been observed. These changes have been attributed to anoxic anoxia.

It has been suggested by van der Molen (167) that cortical cell changes occur at partial pressures of oxygen equivalent to an altitude of 28,000 feet (barometric pressure of 246.8 mm. Hg) and, moreover, that some of these changes might be irreversible. It will be remembered, however, that the average unacclimatized individual cannot live much beyond an altitude of 25,000 feet. Only individuals thoroughly acclimated could withstand an altitude of 28,000 feet; it is known, however, that several members of the various Mount Everest expeditions were reasonably well acclimated to this great height.

Gerard (65), from his studies on anoxia and neural metabolism, has concluded that one of the functions of oxygen is to keep the cell

membrane polarized and, further, that proteolytic processes are initiated by complete anoxia. It is thought that the accumulation of lactic acid in severe degrees of anoxia may be responsible, in part, for this reaction.

It has been suggested by Gellhorn *et al.* (58) that anoxia and hypoglycemia have a similar physiologic action on the central nervous system and that they act synergistically in the production of convulsive seizures. Sugar and Gerard (159), too, have suggested that hypoglycemia acts much like hypoxia on the function of the brain, since it leads to interference with oxidation in that organ.

SURVIVAL TIME OF DIFFERENT NERVE TISSUES DEPRIVED OF BLOOD

Cannon and Burket (32) in 1913 reviewed the literature of the effect of anemia on nerve cells of different classes. Table 14, which

TABLE 14

SURVIVAL TIME OF DIFFERENT NERVE TISSUES COMPLETELY DEPRIVED OF BLOOD*

Tissue	Survival Time (Minutes)
Cerebrum, small pyramidal cells	8
Cerebellum, Purkinje's cells	13
Medullary centers	20–30
Spinal cord	45–60
Sympathetic ganglia	60
Myenteric plexus	180

* From Drinker's *Carbon Monoxide Asphyxia* (New York: Oxford University Press, 1938), p. 133.

was compiled by Drinker (44) from the literature cited by Cannon and Burket, shows the survival time of different nerve tissues when completely deprived of blood.

Drinker, interestingly enough, has pointed out that Table 14 indicates that individuals who have suffered from severe anoxia, such as may be produced by carbon monoxide poisoning, may be practically decerebrated.

Numerous studies (18, 31, 38, 77, 83, 95, 97, 123, 134, 157, 172) have been reported on the effect of acute anemia on the nerve centers. Heymans *et al.* (25) in 1937 studied the problem by perfusion of the isolated head of the dog; the circulation was interrupted for

varying periods of time; and the ability of the centers to revive, after the circulation had been completely interrupted, was noted.

Table 15 shows that the cortical regions are the most sensitive to oxygen want. It is of especial interest to note that the respiratory center, which is generally regarded as being extremely sensitive to oxygen want, may be revived after it has been deprived of its circulation for a considerable time.

Heymans *et al.* (83) pointed out that their experiments demonstrated that the respiratory and circulatory centers possessed great resistance to anemic anoxia and could be revived after the circula-

TABLE 15

ABILITY OF CENTERS AT VARIOUS LEVELS OF THE NERVOUS SYSTEM TO WITHSTAND COMPLETE INTERRUPTION OF BLOOD SUPPLY*

Interruption of Central Circulation up to—	Cortical	Palpebral-pupillary	Cardio-regulatory	Vaso-motor	Respira-tory
1– 5 min.	+	+	+	+	+
5–10	–	+	+	+	+
10–15	–	–	+	+	+
15–30	–	–	+	+	+
30	–	–	–	–	–

* From Drinker's *Carbon Monoxide Asphyxia* (New York: Oxford University Press, 1938), p. 134.

tion had been arrested for as long as 30 minutes. They stated, however, that certain centers, which probably were situated in the cerebrum, were more sensitive to anemia and were irreparably damaged if the circulation were arrested for more than 5 minutes.

Sugar and Gerard (159), studying the brain potentials in cats in which an abrupt and functionally complete anemia of the brain had been produced, reported noticeable differences in the "survival time" and the "recovery time" in various parts of the brain. For example, they found that, following complete anemia, it took 14–15 seconds for the disappearance of potentials in the cerebral cortex, whereas it took from 30 to 40 seconds to make them disappear from the region of the medulla. They wrote as follows:

> The survival time (duration of occlusion necessary to abolish electrical activity) varied four-fold from one brain region to another. . . . . The recovery time (interval between restoration of circulation and return of potentials)

for any structure increases with duration of the anemia and with the number of preceding anemia periods. Under equivalent conditions, the recovery times for various brain regions fall into the same sequence as their survival times.

ABILITY OF YOUNG ANIMALS TO WITHSTAND ASPHYXIA AND ANOXIA

It has been known for a long time that young animals are considerably less susceptible to anoxia and to asphyxia than adults. As early as 1725 Robert Boyle (27) commented on the resistance of kittens to asphyxia, and Paul Bert (23) in 1870 called attention to the fact that newborn animals were capable of withstanding prolonged asphyxia. Since that time a number of observers (7, 88, 95, 97, 138, 139, 151) have reported studies on this phenomenon.

Recently Kabat (95) reported a study of the resistance of very young animals to arrest of brain circulation. Young dogs were found to be much more resistant to acute asphyxia than adult animals. The respiratory center in the newborn animal continued to function seventeen times as long as in the adult, following complete arrest of blood flow to the brain. The newborn also achieved complete functional recovery much more quickly than did the adult animal. At the age of 4 months the resistance was diminished to the adult level. A subsequent report was made by Kabat *et al.* (97). These investigators, by a special technique, produced sudden complete arrest of blood flow in the brain of the dog. The corneal reflex disappeared in 10 seconds, and respiratory functions ceased within 20–30 seconds. If the arrest of the circulation was not longer than 6 minutes, there apparently was complete recovery of function, but stasis for 8 minutes or longer resulted in permanent damage to the brain.

EFFECT OF ANOXIA ON THE CEREBROSPINAL-FLUID PRESSURE AND ON THE INTRACRANIAL PRESSURE

1. *Effect of anoxic anoxia.*—But relatively little investigative work has been reported on the effect of anoxic anoxia on the cerebrospinal-fluid pressure. Several investigators (84, 131, 178) have reported that gaseous mixtures low in oxygen cause an increase in cerebrospinal-fluid pressure. Michelsen and Thompson (124) in 1938 made some observations on human beings of the effect of oxy-

gen want on intracranial pressure. Anoxia was produced by diluting the air in a respiratory chamber with nitrogen until the oxygen content corresponded to a simulated altitude of between 15,500 and 17,000 feet. The subjects were kept in the chamber from 4 to 7 hours. The oxygen saturation in the blood varied from 50 to 70 per cent; it was observed however, that the blood oxygen saturation had no quantitative relation to the severity of the manifestations produced by the low oxygen tension.

The symptoms observed varied a great deal in severity; some subjects complained of mild headaches, and some of excruciating ones. Yawning, sighing, and bradycardia—all typical of increased intracranial pressure—were noted; projectile vomiting, too, was seen, and even semiconsciousness was observed. The investigators felt that the exact mechanism by which anoxia increased intracranial pressure needed investigation.

Yesinick and Gellhorn (178), while studying the similarity of the effects of anoxia and hypoglycemia on animals, also made observations on increased intracranial pressure during anoxia. They concluded that the effects of increased intracranial pressure are due to asphyxia of the medulla rather than to anoxia. This conclusion was based on the fact that if the buffer nerves in the carotid sinus were out, both increased intracranial pressure and asphyxia produced elevation in blood pressure, while anoxia produces falls in blood pressure.

Maurer (122) in 1941 reported that cats exposed to 6 and to 8 per cent oxygen showed an increase in the cerebrospinal-fluid pressure of 1.5–1.1 times the normal, respectively.

Armstrong has reported some interesting experiments of the mechanical effects of decreased atmospheric pressure on the pressures within the canals of the central nervous system. He and his coworkers subjected goats, which were fitted with oxygen gas masks so that they would suffer no anoxia, to decreased barometric pressures. At a simulated altitude of 18,000 feet (barometric pressure of 379.4 mm. Hg) the spinal-fluid pressure began to rise abruptly and continued to do so up to an altitude of 50,000 feet (barometric pressure of 87.3 mm. Hg); after this simulated altitude was reached, the animals were allowed to return to normal atmospheric pressure. These

changes reported in the cerebrospinal-fluid pressure were reported to be independent of anoxia.

Armstrong and his co-workers noted that the intracranial pressure behaved similarly to that of the cerebrospinal-fluid pressure when the goats were submitted to decreased atmospheric pressure. At a simulated altitude of 17,000 feet (barometric pressure of 395.4 mm. Hg) the intracranial pressure began to rise and continued to do so up to the highest simulated altitude attained, namely, 30,000 feet (barometric pressure of 225.6 mm. Hg).

2. *Effect of carbon monoxide on intracranial pressure.*—It has been known for some time that carbon monoxide poisoning is capable of causing a rise in the cerebrospinal-fluid pressure. In 1924 Forbes, Cobb, and Freemont-Smith (52) reported that the experimental inhalation of carbon monoxide produced an increase in the pressure of the cerebrospinal fluid, a congestion of cerebral vessels, and a cerebral edema. Recently Maurer (122), working with cats, found that exposure to 0.5 per cent carbon monoxide caused an average increase of cerebrospinal-fluid pressure 1.74 times that of the normal.

An increased cerebrospinal-fluid pressure following carbon monoxide poisoning has been found in man. Neighbors and Garret (130) found an increase of cerebrospinal-fluid pressure in a man who was unconscious for 10 weeks following carbon monoxide poisoning; after 8 weeks the increase was still present. Forbes (51), too, has reported a rise in a man following exposure to carbon monoxide poisoning.

It is thought that the increased cerebrospinal-fluid pressure and the cerebral edema are the cause of the headache which usually accompanies exposure to carbon monoxide gas.

While the exact mechanism of the increased cerebrospinal-fluid pressure and intracranial pressure produced by anoxia is not known, it is significant that Landis (99) has shown that anoxia may increase the rate of capillary filtration. It is not unlikely that the increased permeability of the capillary wall produced by the anoxia is largely responsible for the increased pressures within the canals of the central nervous system produced by carbon monoxide; this is perhaps also true during anoxic anoxia.

EFFECT OF ANOXIA ON THE SECRETION AND THE COMPOSITION OF THE CEREBROSPINAL FLUID

There are but meager reports in the literature of the effect of anoxia on the secretion or the composition of the cerebrospinal fluid. Nicholson (131) in 1932 reported that air containing a low oxygen tension administered to an animal first produced a noticeable decrease in the flow of the cerebrospinal fluid but that the rate of flow soon returned to normal even though the animal continued to breathe the air poor in oxygen. This suggests the possibility that mechanical effects, produced by the augmented breathing, might have been responsible for the increased flow. High concentrations of carbon dioxide administered either with ventilation under physiologic control or with constant artificial respiration caused an increase in the cerebrospinal-fluid flow. It was concluded that the increased acidity of the body increased the rate of formation of the cerebrospinal fluid. Because of the indeterminate nature of these experiments, however, they should be repeated.

It was reported by Hertzman and Gesell (82) in 1928 that low oxygen tension caused an increased alkalinity of the cerebrospinal fluid. It is thought by some workers, although not by all, that the anoxia produced by carbon monoxide may cause certain changes in the composition of the cerebrospinal fluid. Freemont-Smith and Ayer (54) and Girault and Richard (70) have reported an increase in the protein content of the cerebrospinal fluid following severe carbon monoxide poisoning. The last-named authors also reported a lymphocytosis. In one instance a grossly bloody fluid has been described following poisoning by carbon monoxide (100).

It is thought that the changes of composition of the cerebrospinal fluid following carbon monoxide poisoning are due to the effect of anoxia on the cerebral vessels, since it has been observed (52) that during this condition they show a marked congestion. Since Landis (99) has shown that anoxia affects the permeability of the capillary wall, it is likely that the normal filtration process of the cerebral vessels is disturbed during the anoxia produced by carbon monoxide, so that certain substances enter the cerebrospinal fluid which normally are prevented from entering.

EFFECT OF ANOXIA ON THE FUNCTION OF SMALL UNITS OF THE NERVOUS SYSTEM

1. *Effect on the nerve fiber.*—In 1930 Gerard (64) reported experiments on the response of the nerve fiber to oxygen lack. He reported that asphyxia abolishes the positive potential charge after a negative action potential, that resting potentials are steadily lowered during asphyxia but raised during recovery, and that, when oxygen is readmitted, action potentials in exposed regions rise rapidly to very high values. Lehman (101), working with an excised nerve, found that when it was immersed in pure nitrogen it showed a typical sequence of irritability changes. There was, first, a lowering of the threshold of excitability, which was followed by a progressive failure of irritability of the nerve fiber. The normal functional state was restored if the anoxia did not last too long. It has been shown by Thorner and Brink (164) that if the human ulnar nerve is deprived of its circulation for a period not exceeding 30 minutes a succession of events occurs similar to that described above.

2. *Effect on synaptic conduction.*—Sugar and Gerard (159) point out that it is widely held that the synapse is especially sensitive to oxygen want but that there is no real evidence for this, since it has been shown that synaptic conduction through the cervical sympathetic ganglion can withstand considerable anoxia. In support of this view they cite their own histochemical researches (158), the work of Bronk and Larrabee (30), and that of Bargeton (16).

Bronk and Larrabee (30), working with the stellate ganglion, reported that it could be deprived of its circulation for about 30 minutes before it began to lose its capacity to respond; deprivation of its circulation for approximately 60 minutes, however, caused it to be functionless.

Bargeton (16) in 1938, working with the superior cervical ganglion of the cat, found that, in rather striking contrast to the cells of the central nervous system, the sympathetic ganglion cells showed a marked resistance to deprivation of blood. He observed that complete suppression of blood supply resulted in gradual disappearance entirely of activity of the ganglion; that within 10 or 15 minutes there was total disappearance of activity; but that a large degree of func-

tional recovery returned after the ganglion had been completely deprived of blood for as long as 70 minutes.

3. *Effect on tendon reflexes.*—It has been pointed out by Jokl (92), who was one of the first investigators to study the effect of anoxia on tendon reflexes, that these reflexes are normal until an altitude of about 6,600 feet is reached. Beyond this height, however, they become diminished, and they remain so up to an approximate altitude of 15,000 feet. It seems that this altitude represents a critical level, for above it the tendon reflexes become increased, which, according to Jokl, indicates an early disturbance of nervous control. The author further states that a second critical level exists at about 29,000 feet and that at this altitude loss of consciousness, muscular cramps, paralysis, and death may occur. It is generally believed, however, that the symptoms just named frequently occur at 25,000 feet in unacclimatized individuals.

4. *Effect on the chronaxie.*—As far as the author is aware, no studies have been reported on the effect of anoxic anoxia on the chronaxie of the brain. Several studies have been made, however, of the effect of anemic anoxia on the excitability of the different areas of the cerebral cortex.

In 1927 Rizzolo (142) ligated both carotid arteries and both vertebral arteries in a series of dogs and determined the effect of the anemic anoxia so produced on the chronaxie of the cerebral cortex. He subjected another group of animals to repeated hemorrhages and then studied the chronaxie of the cortex of the brain. He concluded that in neither group of dogs was there any modification of the chronaxie. This was true even in animals which had suffered a pronounced hemorrhage (withdrawal of 200–300 cc. of blood from dogs weighing 6–12 kg.). Occasionally (in two cases out of ten), however, he observed a definite prolongation of the chronaxie following a small hemorrhage (50–100 cc.) in a medium-sized dog. Richard (140), a few years later, using virtually the same technique, confirmed Rizzolo's work.

In 1936 the Chauchards (33) repeated the work of Rizzolo and that of Richard and reached the same conclusion as did these investigators, namely, that there was no change in the chronaxie of the cerebral cortex following ligation of both carotid and both vertebral

vessels. These authors stressed the fact that, even after ligation of these four vessels, the cerebral hemispheres still received considerable blood; and they believed that this explained the reason the chronaxie remained unchanged. They pointed out that local anemia of the cortex produced by compression of the brain caused a prolongation of the chronaxie; if the pressure was reduced, however, and it had not been acting too long, the chronaxie returned to normal. They emphasized that complete interruption of the circulation always produced a decreased excitability of the cerebral cortex; if the circulation had been interrupted for only $1\frac{1}{2}$ minutes, the chronaxie quickly returned to normal, but after $2\frac{1}{2}$ minutes of complete ischemia of the cortex the alteration of the chronaxie persisted.

It is apparent that all workers agree that the blood supply to the cortex may be diminished considerably before there is any change in the excitability of the cells, as indicated by the chronaxie. Since there is some evidence, however, that the chronaxie is not a true measure of excitability of tissues, all this work might profitably be repeated and the strength-duration curve determined. One can only speculate as to what the relationship might be between the excitability of the cortex and the normal physiologic processes which occur in the cells of the cerebrum. It would be expected, however, that there probably is a definite relationship.

In this connection the interesting work of Lennox and the Gibbses (104) may be mentioned. These investigators found that unconsciousness supervenes in man if the oxygen supply to the brain is suddenly reduced so that the oxygen saturation of the blood in the internal jugular vein falls to 24 per cent or less. The subject remains conscious, however, as long as the oxygen saturation does not fall below 30 per cent.

5. *Effect of asphyxia on reciprocal innervation.*—It was shown, in 1939, by Van Harreveld and Marmont (170), working with cats whose spinal cords had been asphyxiated for various periods of time, that after recovery the hind legs showed an exaggerated extensor tone; this usually lasted until death (about 3 weeks). It was concluded that the high extensor tone was caused by a selective damage to the inhibiting system which normally keeps the tone in check.

Van Harreveld (168, 169) studied the problem further and found

that asphyxiation was capable of abolishing reciprocal innervation. He felt that this strongly supported the assumption that asphyxia damages the inhibitory neurones more severely than the excitatory ones.

As far as the author is aware, no studies have been reported of the effect of anoxic anoxia on reciprocal innervation.

6. *Effect of anoxia on conditioned reflexes.*—Andreyev (3) in 1935 ligated both common carotids and both vertebral arteries in dogs and studied the changes in higher nervous activity by the method of conditioned reflexes. He observed that during the first 10–12 days following the operation the temporary disturbances were most marked and were manifested in the complete disappearance of the conditioned reflexes. Later these were often restored. The more delicate functions of the cortex, however, as represented by the formation of long-delayed conditioned reflexes, were eliminated either permanently or for a long time.

In evaluating the results produced by anemic anoxia on conditioned reflexes, it will be remembered that it has been shown that, while anemia produces its effects primarily by anoxia, it produces other changes in the tissues as well. Apparently, no experiments have been reported of the effect of anoxic anoxia on conditioned reflexes.

7. *Effect of anoxia on brain potentials.*—

a) Observations made on animals: The influence of anoxia on the brain potentials of specific brain regions has been studied on animals by a number of workers (10, 17, 20, 28, 29, 42, 136, 152, 159). It is generally agreed by all investigators that effective degrees of anoxia either diminish or eliminate brain potentials. Anoxia often produces some initial stimulation of the brain potentials, but this is quickly followed by a depression.

Prawdicz-Meniniski (136) in 1925 studied brain waves from the motor and visual cortices of curarized dogs and followed them after artificial respiration was suspended. No change during the dyspneic phase of asphyxia was observed, but the potentials increased through the convulsive phase and finally disappeared, although the heart was still beating. Bartley and Bishop (17) in 1933 reported that 3–5 minutes after ligating a superficial artery which supplied the area of

the cortex under observation the potentials disappeared, and Simpson and Derbyshire (152) reported that bilateral carotid occlusion abolished potentials from the cat's motor cortex in 20 seconds.

b) Observations made on human beings: It has been shown by several workers that breathing mixtures of low oxygen pressures can abolish brain potentials in man.

In 1934 Berger (21), working with human beings, reported that the electroencephalogram became more irregular and that larger waves were seen after about 7 minutes' rebreathing from a closed bag with carbon dioxide absorbed.

Gibbs and Davis (67) in 1935 obtained electroencephalograms upon subjects who became unconscious from breathing pure nitrogen. It had been established previously that, normally at rest, frequencies from 10 to 20 per second occurred and attained a maximum of 60 microvolts. The breathing of pure nitrogen caused the frequency of the predominant waves to decrease to between 1 and 5 per second but caused the amplitude to increase about 100 microvolts. These changes occurred gradually and began before the subject lost consciousness. It was also observed that overventilation of the lungs up to the point of clouding of consciousness produced similar alterations in the electroencephalogram. When the subject was allowed to breathe room air, after he had breathed pure nitrogen, a decrease in all electrical activity was noted, followed by a gradual return of the normal waves.

Davis *et al.* (40) in 1938 allowed human subjects to breathe gas mixtures containing 7.8–11.4 per cent oxygen while simultaneous electroencephalograms were recorded. The average voltage increased slightly, but later it decreased and shorter trains of "alpha" waves occurred. Irregular "delta" waves appeared at the time cyanosis was first noticed; and just before consciousness was lost, large "delta" waves dominated the record. These "delta" waves disappeared with the first breath of room air, and the normal pattern was restored in about 2 minutes.

The effect of anoxia on the brain potentials of man, then, is much like it is on lower animals.

8. *Effect of carbon dioxide on brain potentials.*—It has been shown by Lennox *et al.* (103) that carbon dioxide accumulation increases

fast waves, and it is thought that it may, in part, contribute to the augmented high-frequency potentials seen early in anoxia. If there is sufficient excess of carbon dioxide, however, the brain potentials may be abolished, like they are during anoxia.

EFFECT OF ANOXIA ON THE MEDULLARY CENTERS

According to Gasser and Loevenhart (55), the views which have been held regarding the effect of decreased oxidation on the activity of the medullary centers may be classified as follows: (1) Stimulation cannot be produced by decreased oxidation. (2) Stimulation may be produced by decreased oxidation, but only indirectly (as by increasing the stimulating effect of carbon dioxide or by causing formation or accumulation of acid metabolic products). (3) Decreased oxidation itself, under proper conditions, may stimulate the medullary centers.

The last-mentioned view was first advanced by Rosenthal (143) in 1882. Gasser and Loevenhart (55) felt that they had proved definitely that the third view was correct. Their work was done, however, in 1914; and since that time, of course, the function of the carotid bodies has been discovered.

It was shown by Kussmaul and Terrer (98), as early as 1857, that when the blood supply to the brain is completely suppressed, the respiratory center is first stimulated and then depressed. Grove and Loevenhart (74) in 1911 reported that the respiratory center is more sensitive to hydrocyanic acid than the vasomotor center and that the latter is apparently more sensitive than the cardioinhibitory center.

In 1914 Gasser and Loevenhart (55) reported important studies which they had made on the effect of oxygen want on the medullary centers. They pointed out that the stimulation of these centers by oxygen want depends upon three factors: (1) the suddenness of the oxygen want, (2) the extent to which they were decreased, and (3) the condition of the center. Anoxia was produced by the administration of carbon monoxide and by sodium cyanide, and the latent periods of the stimulation of the medullary centers were determined. The latent periods were found to be so short that the stimulation could not be attributed to the accumulation of acid products; so they

concluded that oxygen want itself is a stimulus to the medullary centers.

The oxygen want produced by the carbon monoxide first stimulated the centers and then depressed them; they were stimulated and then depressed in the following order: respiratory center, vasomotor center, and cardioinhibitory center. Their work also gave support to the theory that the activity of the medullary centers depends on the condition of their oxidative processes.

Gasser and Loevenhart (55) pointed out that if cerebral anemia is produced by clamping the cerebral arteries (156) the medullary centers respond in the same manner as they do when subjected to anoxia and, further, that the same relative irritability of the centers has been shown by investigators working on the effect of increased intracranial pressure (49, 129).

In 1919 Lutz and Schneider (109) reported that oxygen want stimulates the respiratory center in man, and in the same year Haldane *et al.* (76) also came to the conclusion that oxygen want per se can act as a stimulus to this center. These reports were made, of course, before the function of the carotid bodies was discovered. It is now thought that oxygen want stimulates the respiratory center indirectly through the chemoreceptors (p. 108). It may be accepted, then, that oxygen want, either directly or indirectly, is capable of stimulating the medullary centers. It is in order now to consider briefly the effect of anoxia on each center.

1. *Effect on the respiratory center.*—The effect of anoxia on the respiratory center has been discussed in some detail in the chapter which deals with anoxia and respiration, and it need not be reiterated here. The reader is referred to page 107.

2. *Effect on the vasomotor center.*—It has been known for a long time that if an animal is subjected to anoxia the vasomotor center is stimulated and that if the anoxia is severe a considerable rise of blood pressure may occur. Mathison (121) in 1911 showed that not only oxygen want but also an excess of carbon dioxide in the arterial blood causes stimulation of the vasomotor center. Anoxia presumably acts either by direct stimulation of the center or reflexly through the sinoaortic nerves. (26). The work of Loevenhart and his associates on this center has been mentioned previously.

Gellhorn and Lambert (59) have pointed out that the present concept of the mode of action of oxygen deficiency and carbon dioxide excess is the same for both respiration and circulation. Carbon dioxide causes stimulation of the "isolated" respiratory and vasomotor center. These authors call attention to the fact, however, that the reactions of these centers to carbon dioxide is different from that of other nerve centers.

3. *Effect on the cardioinhibitory center.*—In 1910 Mathison (120) observed that irregular cardiac slowing occurred frequently during asphyxia in animals with intact vagi. He felt this was due to a stimulation of the cardioinhibitory center. Gasser and Loevenhart, also, as previously mentioned, found that this center was stimulated by oxygen want.

4. *Effect on the cardioaccelerator center.*—It will be assumed, for the sake of convenience in this discussion, that there is an accelerator center, although its definite existence has not been conclusively proved. Nolf and Plumier (132), working with dogs, believed that they obtained some evidence of increased tonus in the accelerator cardiac nerves during asphyxia. Mathison (119), on the other hand, showed that during asphyxia the acceleration which immediately preceded the heart block was not due to stimulation of the accelerator center.

Some evidence has been presented by Sands and De Graff (144) that in progressive anoxia the stimulating effects, up to the period of the crisis (which they found to be produced by 9 per cent oxygen), can be accounted for by the fact that anoxia either depresses the vagi or stimulates the accelerator mechanism. In progressive anoxia, when the vagi are cut, cardiac acceleration is often, although not always, absent; this indicates that the accelerator mechanism may be stimulated. The effect is much the same as if small doses of epinephrine had been administered.

Lutz and Schneider (109), working with man and producing anoxia by the use of both low pressures and low percentages of oxygen, believed they had evidence that anoxia stimulated the accelerator center and that this took place before the cardioinhibitory center was stimulated. They admitted, however, that they could offer no real experimental proof.

It must be emphasized that it is often difficult to interpret experimental results when working on the centers regulating heart rate, since it is known that the heart may be accelerated in at least four different ways: (1) by stimulation of accelerator nerves (or center), (2) by decreasing vagal tone, (3) by secretion of epinephrine, and (4) by an increase in the temperature of the blood (56). Since cardiac acceleration may be produced by several factors, especial care must be exercised before any conclusions are drawn from experimental procedures.

5. *Effect on the vomiting center.*—It has been known for many years that anoxic anoxia may stimulate the vomiting center, since it was noticed early that vomiting often occurred at high altitudes. There are many factors which seem to cause vomiting, and it is difficult to prove exactly by what mechanism anoxia stimulates it.

6. *By what mechanism does oxygen want affect the medullary centers?*—The complete answer to this question is as yet unknown. The extensive researches, during the past few years, on the functions of the aortic and carotid bodies have thrown a good deal of light on this problem, but more work is needed. There is still considerable controversy regarding the relative importance of the various factors which are known to influence the chemoreceptors.

Not only are the chemoreceptors influenced by oxygen want, but the nerve cells of the centers, too, may be affected. Gesell (66) presented evidence several years ago that the cells of the respiratory center could be directly influenced by changes in the hydrogen-ion concentration of the blood. Gellhorn and his associates (59) have shown, moreover, that carbon dioxide may influence certain centers in the medulla. It has also been shown, beyond much doubt, that anoxic anoxia causes a depression of the isolated respiratory center.

Finally, these vital centers may be affected by oxygen want, either reflexly through the chemoreceptors or by direct action on the cells of the centers, in ways which at present are not recognized.

Since, normally, the medullary centers are under strict control of higher neural organizations—for example, the hypothalamic and pontine autonomic centers—it would be of interest to repeat most of the work reported on the effect of anoxia on the medullary centers on the bulbospinal animal. When the early work was done on the effect

of anoxia on the medullary centers, the influence of the higher neural organizations was not fully appreciated.

EFFECT OF ANOXIA ON PSYCHOLOGICAL PROCESSES

1. *Effect of anoxia on the mind.*—

a) Fulminating anoxia: In this type the anoxia is so severe that loss of consciousness may occur without any warning. This may happen when an individual is overwhelmed by noxious gas, such as a miner encounters when he walks into a pocket of methane or carbon monoxide gas. Unless an individual is removed from such an atmosphere almost immediately, he will, of course, die.

b) Acute anoxia: It has been said (12) that acute anoxia resembles alcoholic intoxication; the symptoms are: headache, mental confusion, drowsiness, muscular weakness, and inco-ordination. A person exposed to a low oxygen tension often passes through an initial stage of euphoria, accompanied by a feeling of self-satisfaction and a sense of power. The oxygen want stimulates the central nervous system so that the subject may become hilarious and sing or shout, and other emotional disturbances often manifest themselves.

After a certain length of time this initial stimulation is followed by a subsequent depression; emotional outbursts of a different nature appear; and the personality frequently changes for the worse. Hilarity gives way to moroseness and quarrelsomeness, and the person may become pugnacious or dangerously violent. These latter symptoms are especially likely to occur in anoxia produced by carbon monoxide poisoning. An interesting example of this is given by Haldane (75), who relates that an inspector of mines who had been affected by carbon monoxide gas came out of the mine and shook hands cordially with the by-standers, but when the doctor in attendance offered him his arm, he regarded this as an insult and challenged him to a fight.

Anoxia early affects the higher-centers, causing a blunting of the finer sensibilities and a loss of sense of judgment and of self-criticism. The subject feels, however, that his mind is not only quite clear but unusually keen. He develops a fixity of purpose and continues to do what he was doing when the anoxia first began to affect him, in spite of the fact that it may lead to disaster. This fixity of purpose is high-

ly dangerous, especially when such an individual is responsible for the lives of others, such as is true of an airplane pilot.

Individuals who suffer from oxygen want not only have a fixity of purpose but often make no effort to remove themselves from the zone of danger. This is very well illustrated by a report of Foster and Haldane (53). Sir Clement le Neve Foster, who was chief government inspector of mines in Great Britain, inspected a mine in which a disaster had occurred and became himself a victim of carbon monoxide poisoning. He has given a dramatic account of his experience. He could have walked away from the danger zone, which he himself knew; but he lost his initiative, so that, instead of so doing, he sat down and wrote farewell messages, in which he repeated the word "goodbye" a number of times. It is of interest, further, that a time or two he was inconsistent in spelling the word.

Another example which, among other things, shows loss of interest and initiative is that of Longstaff (106). The purpose of his expedition to the Himalayas was to try, by means of the theodolite, to find the highest point by ascertaining the height of the various peaks. He lost interest in his observations and failed to check his results carefully and critically when he was at great heights, so that the figures were of no value upon his return. He missed, therefore, the main object of his expedition.

A third incident is one which happened to Barcroft himself and which he has related in his monograph (13). He had planned to incarcerate himself for a week in a low-pressure chamber. On the fifth day his wife called to see him and asked him about the barometric pressure. He stated that he had been at a simulated altitude of 18,000 feet and was now at 15,000 feet but, "after all, it made no difference." His wife realized at once that his judgment of what was important had vanished, and the experiment was ended at that point.

The experience of Haldane and Kellas (76) in a low-pressure chamber at 320 mm. Hg barometric pressure (22,000 feet) is of interest in showing the workings of the mind under conditions of acute anoxia. Kellas was an experienced mountaineer and was better acclimated than Haldane. At a barometric pressure of 320 mm. Hg, Haldane, who found that he could no longer write or make observa-

tions, handed his notebook to Kellas. Haldane insisted that the low pressure be maintained, although later he had absolutely no remembrance of it. At a barometric pressure of 350 mm. Hg (20,000 feet) he was handed a mirror, and for some time peered at the back of it. Finally, Haldane consented that the pressure be raised, and at 450 mm. Hg (14,000 feet) his mind became clear and he noticed the power return to his legs. Haldane, himself, admitted that his persistence in keeping the pressure so low was irrational and that he had not intended to do so at the beginning of the experiment.

J. L. Birley (24) has reported several interesting examples of altered judgments of British aviators during the war of 1914–18. One pilot who had been flying at great height found later that he had taken eighteen photographs on the same plate. In another instance a pilot at 19,000 feet cordially waved to an enemy craft and took no further action, although his observer vehemently protested.

These various dramatic instances give a clearer understanding of the effects of anoxia on the mind than could any long or technical discussion. They particularly emphasize the fact that under conditions of oxygen want critical judgment is quite likely to be lost and that initiative, too, may entirely disappear.

c) Aftereffects of acute anoxia: If the exposure to acute anoxia has not been too long or too severe, the aftereffects, although often producing unpleasant symptoms, are only transient in nature and are of no grave consequence. The most common complaint is that of headache; this may come on during the time the subject is actually exposed to anoxia, or it may develop a few hours later. It may be rather intractable and not alleviated by the ordinary analgesic drugs, but after a few hours it subsides of its own accord. Besides headache, other symptoms referable to the central nervous system, such as nausea, muscular weakness, and emotional disturbances may manifest themselves after return to sea-level.

It is thought that repeated exposure to oxygen want may have accumulative effect. Armstrong (4) has stressed this and has described a condition which develops in airplane pilots only, which he has termed "aeroneurosis." He has defined this as a chronic functional nervous disorder characterized by gastric disturbances, nervous irritability, mental fatigue, insomnia, and increased motor ac-

tivity. The exact etiology of this condition is unknown, and oxygen want might be only one factor in its production.

If the subject has been exposed to severe anoxia for too long a time, the aftereffects are often of a formidable nature and may end in death. If death does not ensue, the anoxia may have caused changes in the brain resulting in permanent disability. There are instances on record which indicate that this has happened after prolonged administration of nitrous oxide anesthesia (37, 176).

Recently Thompson and Corwin reported (162) an interesting but heroic study on the postanoxic period. Thompson subjected himself to acute anoxia in a chamber for several hours; for the main part, he was kept at a simulated altitude which ranged from about 11,500 to 17,000 feet. After his removal from the chamber he was in a stuporous or semicomatose state and showed rather alarming postanoxic symptoms. When his respiration failed and artificial respiration became necessary, no concern was expressed, although he was quite aware of its significance. His motor responses were slow, and activity required a great amount of effort; and still more was needed for initiation of effort. There were no delusional or hallucinatory experiences. He stated that it was difficult to tell when the symptoms actually disappeared, but it was several days; and, as a matter of fact, a week or more following the exposure he was still making mistakes in routine laboratory experiments. His observations agreed with those of Haldane, that mental and physical aberrations were more severe after exposure to anoxia.

d) Aftereffects of carbon monoxide poisoning: Grave aftereffects are not uncommon following exposures to carbon monoxide. Whether this is due to the fact that it produces both anemic and histotoxic anoxia is unknown. The patient does not recover at once, as he does following short exposures to anoxic anoxia; or, if he does recover, he may regain only partial consciousness and then lapse again into unconsciousness. Marked spastic conditions of the muscles and an occasional epileptiform seizure have been described. The patient may linger on for days in a semicomatose condition with spastic muscles and occasionally opisthotonos. When consciousness supervenes, loss of memory, mental incapacity, or even mania sometimes occur. If the patient survives the first few days, the symptoms will generally

pass away, and he will recover, except in those instances where organic changes have taken place within the central nervous system. Occasionally a peripheral neuritis occurs.

Pathologically, gross hemorrhages, as well as small multiple hemorrhages, in the brain have been described.

e) Chronic anoxia: While the effect of acute anoxia on the body resembles alcoholic intoxication, that of chronic anoxia simulates fatigue, both mental and physical (12). Since the effect of oxygen want on the central nervous system is under consideration, this discussion will be limited chiefly to the effects on the mind.

People living at high altitudes for long periods of time become acclimated. The question of acclimatization, however, has been considered in some detail (p. 140). It has been pointed out that certain compensatory factors are brought into play which greatly aid the body in withstanding the low partial pressures of oxygen so that the subject can live with a greater degree of comfort and do his work more easily. These compensatory factors, however, are not equally effective in all individuals. The mental and physical health of some individuals often remain indifferent; they become irritable and do not get along well with their fellow-men; they may show a mild mental depression and often lack the ability to concentrate. Mental tasks are harder under conditions of oxygen want, and mistakes are more frequent. Recovery from mental fatigue, too, is slower than it is at lower altitudes. Many of these people, furthermore, are unable to obtain a refreshing sleep; their nights are often restless and disturbed by dreams. This lack of restful sleep also tends to keep their health constantly under par. A return to lower altitudes, of course, will restore normal health to these people, and, indeed, they often find it necessary to take periodic sojourns at sea-level.

2. *Miscellaneous studies of the effect of anoxia on psychological processes.*—Within the limits of this monograph it is not feasible to discuss in detail the wealth of work which has been reported on various psychological studies made during oxygen want. Many of these have been made on aviators, but miscellaneous experimental studies have been made also on human subjects not necessarily in the interests of aviation. In the discussion which follows, the studies made on aviators will be considered first.

a) Studies made on aviators:[1] Until the year 1914, but little work had been reported on the effect of anoxia on psychological processes, but during the war of 1914–18 numerous psychological studies were made on aviators by a number of workers (2, 8, 9, 24, 36, 43, 46, 50, 81, 91, 110, 133, 157, 163, 177).

Dunlap (46) has summarized the findings of these early studies on pilots as follows: (1) The primary and important psychological effects of oxygen want are on voluntary co-ordinarion and attention. (2) Sensitivity and perception remain efficient until anoxia curtails the ability of the subject to attend to stimuli. (3) There is no reduction in speed of simple reactions. (4) There is no falling-off of rapidity in discrimination except that due to deficiency of motor control. (5) Memory and other higher mental processes are not affected until muscular inco-ordination produces distractibility or until the ability to attend to details in learning is decreased. Finally, it is suggested that the effects of anoxia produce a change in the integrative action of the nervous system rather than any change in the irritability or efficiency of any part.

Bagby (9) in 1921 reported some of the significant results of the work done in the Medical Research Laboratory of the United States Army. The subjects used in these experiments were exposed to anoxia by the use of the Henderson rebreathing apparatus (p. 23). He summarized the findings as follows:

(1) Motor performance: Progressive anoxia caused muscular tremor, inco-ordination, and overdischarge. These became worse as rebreathing proceeded, because of a loss of integration of the central nervous system.

[1] Reports of the early work done on aviators may be found in *Air Service Medical* (Washington, D.C.: U.S. Government Printing Office, 1919), Part II, chap. vii, "Psychology Department," pp. 293–330, (2).

In 1921 F. C. Dockeray and I. Isaacs published a résumé of the psychological research done in aviation: "Psychological Research in Aviation in Italy, France, England and the American Expeditionary Forces," *Journal of Comparative Psychology*, I, No. 2 (April, 1921), 115–48. Recently R. R. McFarland has reviewed the literature on effects of oxygen want on certain psychological processes in balloonists, aviators, and mountaineers in "The Psychological Effects of Oxygen Deprivation (Anoxemia) on Human Behavior," *Archives of Psychology*, No. 145 (1932). Still more recently he has reported studies made in the Chilean Andes in "Psycho-physiological Studies at High Altitudes in the Andes," *Journal of Comparative Psychology*, Vols. XXIII and XXIV (1937).

(2) Attention phenomenon: The anoxia produced a lowering of the subject's distractibility, so that a marked reduction developed in the ability to carry on a number of discrete tasks simultaneously. When the anoxia became severe, the subject was unable to concentrate on any task in a normal manner.

(3) Condition of resting muscles: The observations were made on the left hand; the muscles first relaxed, then became tense, and finally became twitchy.

(4) Removal of inhibitions: The subjects often manifested uncontrolled anger, but in milder forms they showed an attitude of resentment. The type of reactions varied, since some of them became silly and some even went into fits of uncontrollable laughter.

(5) Self-observation: Many subjects stated that they could "pull themselves together" for a short time, but then they "wanted to rest."

It hardly needs to be emphasized that the various psychological studies made on aviators have been of great practical value. They have aided materially in the selection of pilots both for army and for commercial planes and have emphasized, among other things, the importance of the factors of fatigue, staleness, and ill-health in airplane pilots.

b) Miscellaneous studies: Barcroft (14) relates that a few mental tests were made on the members of his South American party (1921–22) at Cerro de Pasco (altitude 14,200 feet). The conclusion was that the tests given were too simple to be of real value. It was observed, however, that the effort of mind needful to do the tests was more pronounced than the loss of accuracy with which they were done.

Hingston (89), medical officer to the 1924 Mount Everest Expedition, gave simple mathematical tests to members of the party at 7,000, 14,000, 16,000, and 21,000 feet. Apparently making increased effort, the men did very well on these tests. McFarland believes that the tests probably were too simple to show subtle incapacities. It is to be remembered also that the tests were made on fairly well-acclimated subjects.

Lowson (108) in 1923 reported some studies made on the effect of oxygen want on certain psychological processes. He concluded that until the diminution of oxygen reached 50 per cent of the nor-

mal, there occurred in the average subject no significant alteration in behavior; beyond this, however, the changes were rapid and great.

Tanaka (160) in 1928, working with a low-pressure chamber under Haldane's direction at Oxford, reported work done on six subjects. He tested speed in simple and complex sorting, addition, memory, and strength of grip at different altitudes up to 21,000 feet. He concluded (1) that anoxia caused a deficiency in both mental and physical work; (2) that there was considerable difference as to the altitude at which changes occurred; (3) that anoxia caused a greater deficiency in mental than in physical work; (4) that anoxia affected especially the quality of work; and (5) that the usual critical point where sudden changes occurred was 428 mm. Hg (15,000 feet altitude).

McFarland (112) in 1932 made exhaustive studies of oxygen want on psychological processes. In his work he used a spirometer and oxygen mixtures ranging from 11.43 (17,000 feet) to 7.68 per cent (28,000 feet), and he came to the following conclusions: (1) Simple sensory and motor responses were not seriously impaired until the oxygen want was so severe that the subject approached collapse (about 24,000 feet [8.87 per cent oxygen]); vision and kinesthesis (muscle sense) were the first to be affected, and hearing the last. (2) Choice reactions appeared to be impaired before simple reactions. (3) Neuromuscular control was impaired before the loss of capacity in more highly organized functions, such as choice reactions. (4) There was a loss of memory with oxygen percentages as low as 9.05. (5) Concerning the effect on attention, anoxia, by eliminating extraneous factors, apparently facilitates attention but handicaps it when it undermines voluntary co-ordination. (6) Anoxia impairs higher mental powers. (7) Anoxia affects feelings or moods, depending on the length of time the individual is subjected to anoxia and other factors; it may stimulate or depress. (8) It was concluded, also, that significant data relative to the basic patterns of personality could be obtained under severe oxygen want.

McFarland (113) in 1937 reported observations on psychological studies made during a sudden ascent to 15,000 and 16,500 feet on trans-Andean planes and during slower ascents by train, also in the Andes, to somewhat lower altitudes. From his observations he concluded that the rate of ascent was an important variable and that

there was a significant impairment of both simple and complex psychological functions at these altitudes. He found that, on the whole, the mental tests which involved complex reactions were most affected by high altitudes; the motor tests were affected less; and the sensory tests least of all.

c) Studies made on subjects undergoing acclimatization: In a subsequent paper McFarland (114) reported sensory and motor tests on ten subjects undergoing acclimatization during a 3-month period at various levels up to an altitude of 20,140 feet. The following sensory and motor tests were given: (1) auditory thresholds (for eight frequencies); (2) phoria test for ocular muscle balance; (3) fatigue of accommodation and convergence; measurement of afterimages; (5) color-naming test; (6) simple and choice reaction time; (7) dotting test of neuromuscular co-ordination; and (8) mirror test. He found a variability of response for both the individual and the group at 15,440 feet and above, and a significant difference in the means for the group at 17,500 feet and above.

He also reported (115) on the following psychosomatic tests, using the same subjects and the same altitudes: (1) speed of apprehension for words, (2) judgments of duration, (3) repetition of auditory patterns, (4) perseveration tests, (5) memory tests, (6) code transliteration, and (7) Thorndike C.A.V.D. intelligence test.

At 15,440 feet differences in the means and variability in the mental tests were observed; these became more marked at higher altitudes. There was a close parallel to the periods of greatest discomfort in adaptation to the altitude and the psychosomatic changes or psychological complaints.

It appears, from the observations of McFarland, that in fairly well-acclimated subjects psychological processes for practical purposes are not affected until an altitude of approximately 15,440 feet is attained. It will be recalled in this connection that Barcroft stated that at Cerro de Pasco (14,200 feet) mental tests gave indeterminate results. Any psychological tests made, moreover, on acclimated subjects on Pike's Peak (14,100 feet) probably would also show no positive results.

d) Most common psychological alterations in behavior: It is of distinct interest to call attention to the ten most common psycho-

logical alterations in behavior which McFarland reported. These observations were made on members of the International High Altitude Expedition to Chile. In order of frequency, they were as follows: (1) greater effort to carry out tasks, (2) more critical attitude toward other people, (3) mental laziness, (4) heightened sensory irritability, (5) sensitiveness on certain subjects, (6) dislike of being told how to do things, (7) difficulty in concentrating, (8) slowness in reasoning, (9) frequent recurring ideas, and (10) difficulty in remembering.

These alterations in behavior reported by McFarland fit in very well with early observations made by Barcroft, Haldane, and others. It must be remembered, however, that McFarland's observations were made on ten subjects only and that these were a highly selected group. These identical alterations in behavior, in the same order of frequency, probably would not be found in an unselected group of subjects.

McFarland reported that no significant correlations between mental tests and biochemical determinations were found. The correlation between mental tests and physiological measurements at high altitudes, however, revealed a number of positive relationships.

3. *Influence of anoxia on dreams.*—Since dreams are deemed of great importance by psychoanalysts and since they are so often mentioned in the literature which deals with high altitudes, the effect of anoxia on dreams will be considered briefly.

Most writers emphasize the disturbances of sleep experienced by unacclimatized subjects at high altitudes. It has been pointed out by Monge (125) that native Andeans accustomed to living at great heights complain of restless sleep and disturbing dreams when they suffer from an attack of chronic mountain sickness (Monge's disease). Dr. Crane, medical officer for the Cerro de Pasco Copper Corporation, has observed that newcomers to Cerro de Pasco (12,000–14,200 feet) experience unrefreshing sleep and fantastic dreams, which are often imaginative and apprehensive in character.

Probably the most interesting and comprehensive observations of the effect of high altitudes on dreams are those made by McFarland (115). He has reported in some detail the dream experiences of members of the International High Altitude Expedition to Chile. He re-

lates that, prior to the ascent of the high plateau region, the dreams of the members were generally associated with home situations and with vivid experiences close at hand; they were also featured by sexual or anxiety situations.

When the members of the expedition first ascended the high altitudes, that is, before acclimatization took place, they experienced dreams which were fantastic and illusory in nature—they presumably had the usual experience of newcomers to high altitudes. When they reached their stations, situated at very high altitudes (17,500 and 21,140 feet), and were by this time presumably fairly well acclimated, they dreamed infrequently, and there was but little consciousness of sex.

Perhaps the most interesting observation made was that the dreams which accompanied the greatest physiological disabilities were usually the most vivid and fantastic. McFarland has expressed it thus: "Variations in the general physiological state, therefore, appeared to be equally as important as inner conflicts or motives, considered by many to be the basic course of dreams." The psychoanalysts probably would find it hard to reconcile this with their concept of the significance of dreams. It is of interest at this point to mention that several illnesses, especially those associated with gastrointestinal disturbances of any kind, may produce disturbing dreams. Sufferers from migraine often experience disturbing dreams the night preceding an acute attack. This lends evidence to the statement made by McFarland.

4. *Résumé of the effect of anoxia on psychological processes.*—Little need be said in résumé of the effect of anoxia on psychological processes, since a brief review has been presented previously of the many observations made. For practical purposes these psychological tests are most important for airplane pilots. One important finding is the great individual variation which may occur. This indicates, of course, the need for careful selection of pilots.

More work should be done on the effects of anoxia on psychological processes during slight indisposition. While, in general, it is known that anything which lowers the efficiency of pilots makes them more susceptible to oxygen want, more work is needed to ascertain what effect relatively slight indispositions may have on

them. There are a number of these, such as a cold, headache, slight gastrointestinal disturbance, toothache, and others, which ordinarily do not incapacitate a man for work but which, nevertheless, greatly decrease his efficiency. Besides these organic complaints, there are more subtle ones, such as domestic difficulties and financial worries, slight alcoholic excesses, and others—all of which may affect the psychological process as well as the mental powers. It is likely that anoxia exaggerates all these complaints, so that, while some of these might be trivial to a man engaged in routine work, they may assume relatively vast proportions in men subjected to anoxia.

Recently, Barach (11) has insisted that no pilot who is responsible for the lives of others should fly above 12,000 feet without oxygen. His views have been criticized; but theoretically, for the unacclimatized man, he probably is correct. It must be remembered also that these pilots may not always be in prime condition and that occasionally they may have some of the indispositions mentioned above. On the other hand, a pilot who is in excellent physical condition and who is probably partly acclimatized should be able to pilot a plane safely at 12,000 feet.

EFFECT OF ANOXIA ON REACTION TIME

It is necessary to distinguish between "simple reaction time" and "choice reaction time." By the former is meant the time which elapses from the moment the stimulus is given until the response occurs. Choice reaction time, however, requires judgment; since the subject must choose whether or not he is to respond to a given stimulus, more synapses are involved, and the time is normally longer than the simple reaction time.

A number of studies have shown (19) that anoxic anoxia produces only slight retardation of simple reaction time until an altitude of about 20,000 feet (barometric pressure of 360 mm. Hg) is reached; this is about the point of psychomotor collapse in the unacclimatized subject. In 1911 Durig and Reichel (47), performing experiments on Monte Rosa (15,000 feet) on subjects who had been there 8 days, and again after 16 days' sojourn, reported a possible loss in auditory reaction time, although they admitted their results were indeterminate. In 1893 Mosso (127) had reported somewhat similar re-

sults. In 1935 Jongbloed (94), using a low-pressure chamber, found that at a simulated altitude of 5,000 meters (16,404 feet) choice reactions were significantly lengthened. Stern (155) in 1926 found that newcomers on Davos (5,100 feet) and at an altitude of 8,400 feet showed a prolonged reaction time which was shortened by oxygen inhalation.

Tanaka (160) in 1928, using a low-pressure chamber, and McFarland (112) in 1932, using a Douglas bag, observed a significant loss in speed and accuracy in choice reaction time above 15,000 and 18,000 feet. Bonnardel and Liberson (25) in 1932 on the Jungfraujoch (13,670 feet) found no significant changes in either visual or auditory reaction time.

McFarland (114) feels that studies showing slow reaction time which have been reported below 14,000 feet probably have been performed following a rapid ascent, so that the element of fatigue is added. In 1937 he (113) reported determinations made of choice reaction time of six subjects at Lima (sea-level) and Morococha (altitude 14,890 feet). Expressed in hundredths of a second, the mean for the six subjects at Lima was 53.7 and at Morococha 60.3.

In a later paper (115) McFarland reported studies made on sensory and motor responses on subjects during acclimatization in the Chilean Andes. No significant differences were observed in the simple reaction tests until an altitude of about 20,140 feet was reached. Variability of responses were, however, reliably increased at 17,500 feet. The choice reaction time was significantly impaired at 17,500 feet.

In a subsequent paper (116) studies made on simple and choice reaction time on native miners in the Chilean Andes at an altitude of 17,500 feet were reported; the reaction times were prolonged and the responses more variable in these men than in workmen at sea-level. The differences were statistically significant.

EFFECT OF ANOXIA ON NEUROMUSCULAR CONTROL

Hingston (89), medical officer to the 1924 Mount Everest Expedition, reported mild tremor of eyelids and fingers at 14,000 feet in one subject and at 21,000 feet in another. In 1925 Stern (154) found an increase in hand tremor at altitudes of 5,100 feet (Davos) and at

8,400 feet. Loewy and Wittkower (105) in 1933 at similar altitudes described an increased reflex irritability in seven of nine subjects and also noted unusually active responses to Chvostek's sign and Trousseau's phenomenon.

Jongbloed (93) found that at a barometric pressure of 150 mm. Hg animals showed catatonic reactions similar to those produced by bulbocapnine. McFarland (112), using a Douglas bag, observed that at a simulated altitude of 17,500 feet increased muscular tremors and a loss of neuromuscular control in handwriting tests occurred; and he reported, further, that at a simulated altitude beyond 19,500 feet the loss of efficiency was sudden and great. Goralewski (73) in 1935, using a low-pressure chamber and requiring the subjects to reproduce geometrical figures and sentences, noticed an impairment in this ability in a number of subjects at oxygen percentages at 14–18; this impairment was increased at lower oxygen pressures.

McFarland (114), working with subjects during acclimatization, found that in the dotting test for neuromuscular co-ordination, there was no sign of loss of efficiency until an altitude of 15,440 feet was attained.

1. *Observations made on natives at high altitudes.*—McFarland (116) used the dotting test for determination for neuromuscular co-ordination on natives in the Chilean Andes residing at an altitude of about 17,000 feet. The difference between the means of men working at sea-level and the natives at high altitudes on the test for neuromuscular co-ordination were not statistically significant. Responses of the natives of high altitudes, however, were more variable.

2. *Effect of anoxia on handwriting.*—Many investigators have studied this problem, since it is a practical and easy method of studying muscle control. In general, it may be said that the more severe the anoxia, the greater the loss of the ability to write normally. Figure 17 shows specimens of handwriting at different oxygen percentages up to 7.68 (altitude 28,000 feet). It is readily seen that as the anoxia progresses in severity the handwriting becomes less legible.

3. *Type of paralysis produced by acute anoxia.*—In severe anoxia an ascending type of paralysis is produced. The legs first lose their power, so that the subject is unable to stand; as the paralysis ascends, the arm muscles soon become affected; the neck muscles are

The pencil numerals are just the last two figures of the chronoscope reading. Ink numerals are the exact durations of command reactions by subtraction of pencil record from last in order, adding 10 when necessary.

NORMAL

Curious slowing up of reflex. Seemed to be an appreciable delay before I could get response going. It was like a slight "hitch." Seemed to be a slight vertigo in upper frontal part of head & by slightly further exposure. Seemed to be slightly more than hitherto.

11.0250$_2$ – 16,000 FT. ALTITUDE

Unaccountable failure of discrimination rather silly feeling. quite cracked up after a period of lethargy aroused out of proportion by feeling that the higher I got the better I got. aroused at thought of Eiffel Tower & better etc so abstract hysterical.

11.0250$_2$ – 18,000 FT. ALTITUDE

Seem to get fatigued rapidly during course of test. Have to rest myself by brief rest between each exercise & strike key

10.2850$_2$ – 20,000 FT. ALTITUDE

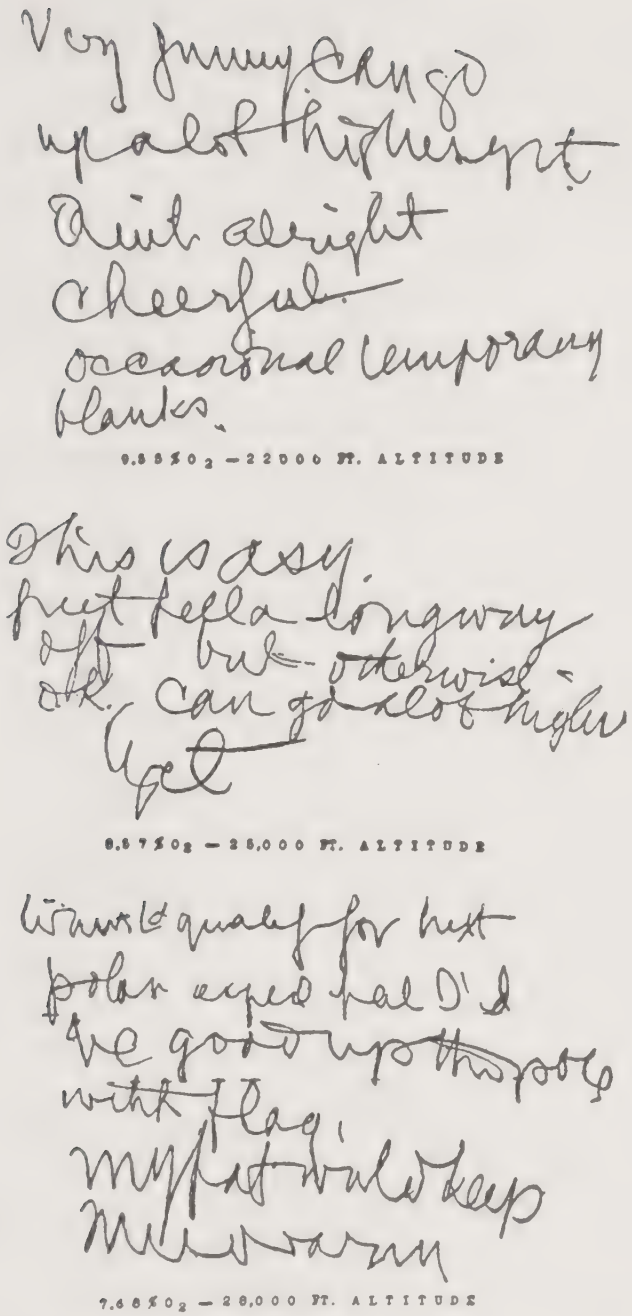

FIG. 17.—Specimen of handwriting at the oxygen percentages and corresponding altitudes indicated. (From McFarland, "The Psychological Effects of Oxygen Deprivation on Human Behavior," *Archives of Psychology*, No. 145 [New York, 1932], pp. 110–11.)

the last of all to be involved. That anoxia produces an ascending type of paralysis was dramatically illustrated in the case of Coxwell when he made the famous balloon ascent with Glaisher. Coxwell's muscles were, for the main part, paralyzed, except those of his neck; he could still move his head, and so he was able to grasp the rope valve with his teeth and, by so doing, saved his life and that of his companion.

Another dramatic instance of muscular paralysis due to oxygen want is that of the experience of Tissandier, sole survivor of the three scientists who ascended in the balloon "Zenith." At great heights he realized that he needed oxygen, but he could not husband the strength to raise the mouthpiece of the oxygen container to his lips.

Finally, it may also be mentioned that often individuals suffering from carbon monoxide poisoning become paralyzed, so that, although they are conscious and wish to leave the zone of danger, they are physically unable to do so.

EFFECT OF ANOXIA ON THE AUTOMOMIC NERVOUS SYSTEM[2]

A comparatively limited amount of work has been reported on the effect of anoxia on the autonomic nervous system. It has been held by Cannon for many years, however, that the sympatho-adrenal system played an important role in the adaptation of an animal to anoxia; a part of his "emergency theory" was built on this concept. Dr. Cannon firmly believes that anoxia is capable of producing an increase in the flow of epinephrine and explains many of the phenomena produced by anoxia as being due to this mechanism. He has suggested (personal communication), for example, that the retardation of gastric emptying produced by anoxia (p. 162) can be accounted for by an increased release of epinephrine.

According to Sawyer *et al.* (146), if normal cats are exposed to an oxygen tension of 6 per cent, they will live for at least an hour. Cats which have had the greater part of their autonomic nervous system removed, however, will collapse within 15–38 minutes. This work supports Cannon's early views.

[2] The reader is referred to the sections which deal with the effect of anoxia on the adrenals (p. 190) and on the blood sugar (p. 64).

It is believed by Monge (126) and by Aste (6) that residents of high altitudes show a hypertonus of the autonomic nervous system. Monge, by stimulation of the oculocardiac reflex, observed an increased tonus of the vagus nerve, and compression of the solar plexus gave a similar response of the sympathetic nerve. Aste, by intravenous injection of atropine in twenty-five soldiers who lived in the high Andes, also demonstrated a hypertonus of the vegetative nervous system. According to McFarland (115), Dr. Crane, chief surgeon at the Cerro de Pasco Mines in Peru, found that, in order to produce an effect on the circulation equal to that seen at lower levels, it is necessary to inject twice the amount of atropine.

Ury and Gellhorn (166), working with rabbits, reported that 6–8 per cent oxygen raised the threshold for pupillary reflex dilatation produced by weak stimulation of the sciatic nerve. These authors suggested the possibility that this might have been produced by inhibition of the parasympathetic, and pointed out that, if this were true, both excitatory and inhibitory processes in the central nervous system are diminished under the influence of anoxia.

In summary, it may be said that undoubtedly anoxia is capable of influencing the autonomic nervous system. The effects of anoxia on the alimentary tract, on the kidneys, on the sphincter pupillae of the eye, on the carotid sinuses, and, perhaps, on other tissues probably can be explained, in part at least, by its effects on the nerve supply to these various organs.

EFFECT OF ANOXIA ON THE SPECIAL SENSES

1. *Effect of anoxia on the eye.*—Balloonists first called attention to the fact that at high altitudes accommodation was affected and that they experienced difficulty in reading the mercury column, although distant vision was unaltered.

Wilmer and Berens (173) in 1918, making quantitative studies of vision, found that judgment of distance, size of visual fields, accommodation, convergence, and retinal sensitivity were impaired at oxygen pressures corresponding to an altitude of 20,000 feet. Slight differences at 15,000 feet were noted, but none at 10,000 feet. Goldman and Schubert (71) and Sauer (145) obtained similar results. Barcroft (15) relates that several members of his South American party

experienced visual disturbances at Cerro de Pasco (altitude 14,200 feet).

Many observers have noticed a decrease in the threshold for brightness produced by anoxia. Bert (22) called attention to this many years ago, and the reports of balloonists also emphasize it. Schubert (150) has recently reported a considerable decrease in the threshold for brightness and a lessening of the field of vision in experiments performed in a low-pressure chamber at altitudes above 21,000 feet. Gellhorn and Spiesman (61), using oxygen mixtures from 11 to 9 per cent (17,000–22,000 feet), observed a decrease in visual intensity and discrimination. The presence of nystagmus (62) also was observed. In a later paper (57) Gellhorn reported that if 3 per cent carbon dioxide is given along with 8 or 9 per cent oxygen there is but little diminution of visual intensity discrimination, whereas if the carbon dioxide is not given the latter is quite marked. He believed this was due to the circulatory improvement induced by the carbon dioxide during the oxygen deficiency.

a) Oxygen deprivation and visual fields: The work of Wilmer and Berens has been mentioned. In 1938 Evans and McFarland (48) reported that central visual acuity remained unaffected even at the peak of oxygen deprivation and that, except for a region from 8 to 10 degrees about the macula the angioscotoma widened with progressive oxygen deprivation until it obliterated the visual field. Since ephedrine sulphate, which causes vasoconstriction and a rise in blood pressure, is often given in conditions associated with angioscotoma brought about by venous stasis, the authors suggested that similar medication might be of benefit to aviators who suffered from visual disturbances produced by anoxia.

b) Effect on eye movements: McFarland *et al.* (118), studying the effects of oxygen deprivation on eye movements in reading, found, among other things, that if the oxygen content was diminished to about 12.5 or 10 per cent, there was an increase in reading time and in fixation and a marked diminution of qualitative movements. Rhythmical nystagmoid movements also appeared.

c) Effect of high-altitude disease: Monge (125) in 1929 reported that in permanent residents of the high plateaus of South America a variety of disorders of the sense organs occurred. In chronic moun-

tain sickness (Monge's disease) these were accentuated. In severe cases a considerable dilatation of the capillaries of the retina has been described by Dammert (41). It is of interest, in this connection, that recently Cusick, Benson, and Boothby (39) reported that at an altitude of 18,000–21,000 feet the retinal vessels dilate. In what Monge termed "subacute mountain sickness," he found a diminution of visual acuity and a cloudiness of vision.

d) Effect on negative after-images: Gellhorn and Spiesman (63), using a Douglas bag to produce anoxia, found a lengthening of the latent period of negative after-images following the inhalation of an oxygen mixture from 11 to 9 per cent (17,000–22,000 feet). It was found that the effect lasted as long as 12 minutes after the readmission of air.

In airplane ascents from 15,000 to 16,500 feet McFarland (113) found a lengthening of the appearance and disappearance of negative after-images of 43 and 46 per cent, respectively, after one flight.

e) Dark adaptation under reduced oxygen tension: In 1935 Tanaka and Sekiguchi (161) reported that low barometric pressure caused a decrease in dark adaptation. McFarland and Evans (117) in 1939 reported, further, that oxygen deprivation elevated dark-adaptation curves. By inhaling oxygen these effects were counteracted within 2 or 3 minutes. They concluded from their work that the effects were of no great practical significance in relation to night blindness in a pilot until altitudes of 10,000–12,000 feet were attained. They felt, further, that the changes produced by oxygen want were not concerned with the photochemical substances of the retina but with the neural elements of both the retina and the central nervous system.

f) Anoxia and dark adaptation in vitamin A deficiency: McDonald and Adler (111) in 1939 reported work on the effect of anoxia on dark adaptation in vitamin deficiency. They found that the threshold rise due to anoxia was additive and was the same in the normal and in the vitamin A deficiency state. Since it is known that vitamin A is concerned with the photochemical basis of the visual response, they felt it was probable that anoxia acted elsewhere on the visual system, namely, on the nerve mechanism. These workers had more proof for this conclusion than did the workers mentioned above.

g) Effect of anoxia on intraocular tension: As early as 1918 Wilmer and Berens (173) stated that there was no correlation between the intraocular tension and various cardiovascular changes produced by high altitudes. Recently it has been reported by Pinson (135) that anesthetized rabbits subjected to a simulated altitude of 40,000 feet showed no appreciable alteration in the intraocular pressure. This finding is of distinct clinical importance, since, if anoxia caused a rise in intraocular pressure, it would be hazardous for individuals suffering from glaucoma to subject themselves to high altitudes.

2. *Effect of anoxia on hearing.*—In progressive anoxic anoxia the sense of hearing is the last to disappear. Lewis (80) in 1918 and Bagby (9) in 1921, using the rebreather method for inducing anoxia and also the low-pressure chamber, could detect no change in hearing due to oxygen want until all the other higher cerebral centers were impaired or just before collapse took place. In 1904 Agazzotti (1), working with a low-pressure chamber, had reported, however, a decrease in auditory sensitivity both in human beings and in guinea pigs at an altitude of 16,000 feet (420 mm. Hg barometric pressure).

Barcroft (15) reported that some of the members of his expedition suffered from auditory disturbances at Cerro de Pasco (altitude 14,200 feet); and Richter (141), during a Himalayan expedition, had noticed alteration in hearing.

Using the Douglas bag for inducing anoxia, Gellhorn and Spiesman (61) in 1935 reported that if 10 per cent oxygen or less were inhaled for 10–30 minutes there was a decrease in the hearing threshold (which often lasted for several hours), depending upon the severity of the anoxia, the duration of the experiment, and the sensitivity of the subject.

McFarland (113) in 1937 reported that the auditory threshold for eight different frequencies was about twice as high at Morococha (14,890 feet) as at Lima (sea-level). In a subsequent paper (114) in which he reported studies made during acclimatization he found that at 17,500 feet the threshold for the four highest frequencies was significantly increased.

Observations made on natives of high altitudes: Raffo (137) in 1934 reported a decrease in auditory sensitivity in residents of the

Andes at an altitude of 13,600 feet. He also found a heightened sensitivity to artificial stimulation of the vestibular apparatus.

Studies made on the auditory threshold by McFarland (116), on native residents in the Chilean Andes (altitudes from 17,000 to 15,000 feet), showed that the threshold was 6–8 decibels higher than for workmen at sea-level; the results were statistically significant. The variability of response was also greater in the high-altitude group.

3. *Effect of anoxia on taste and smell.*—No well-controlled experiments of the effect of anoxia on either taste or smell could be found in the literature. These two special senses are so closely associated that, unless especial precautions are observed when experiments involving either one are performed, any results reported must be accepted with hesitation.

Hingston (89), medical officer for the 1924 Mount Everest Expedition, reported that at an altitude of 19,000 feet two members of the expedition noticed an impairment of the sense of taste. When they descended to 16,500 feet, taste was restored. Richter (141), during a Himalayan expedition in 1932, reported alterations in taste at an altitude of about 16,500 feet.

No reports in the literature could be found dealing with the effect of anoxia on the sense of smell. It may be that during the observations of the effect of high altitude on taste, just quoted, smell, too, was affected by the anoxia. More well-controlled work is needed on the effect of anoxia on both taste and smell.

While such a study might appear to be one of academic interest only, it is worth while recalling that occasionally patients who have suffered a skull injury lose their sense of taste. This distressing condition may be but transient in nature, but sometimes is permanent. It is possible that in these latter cases the skull injury may have damaged irreparably the blood vessels supplying the gustatory center, so that the loss of taste is due to a local anemic anoxia.

4. *Effect of anoxia on tactual sensitivity.*—The effect of altitude on tactual sensitivity was studied by Loewy and Wittkower (105) following an ascent without physical strain from an altitude of 5,100

feet (Davos) to one of 8,700 feet. An increased effect was noted in the dermographic and chemical stimuli; the sensitivity to pressure on the skin, moreover, was slightly impaired, as was the two-point threshold. The explanation they gave for their findings was that the oxygen want, by stimulating the vasomotor center, caused a peripheral vasoconstriction. It seems, however, that this work needs confirmation, since the oxygen want at 8,700 feet is but slight and probably would have no effect whatsoever on the blood pressure.

Hartman (78), in acclimatized subjects in the Himalayas, found that below an altitude of 23,000 feet sensitivity was not impaired. He felt, from experimental evidence obtained from work in a low-pressure chamber, that in nonacclimatized subjects the critical changes in skin sensitivity occur at altitudes approximately 5,000 feet lower than in acclimatized subjects. According to his work, then, changes would not occur in the average person until a height of 18,000 feet was attained. This, indeed, seems more likely than the findings reported by Loewy and Wittkower given above

5. *Résumé of the effect of anoxia on the special senses.*—From the practical standpoint of the effect of anoxia on the special senses, the effect on the eye is doubtless the most important. There is evidence that there is a loss of accommodation and loss of visual acuity at altitudes at which pilots fly. There is also evidence that there may be some persistent aftereffects if the pilot has subjected himself to extreme altitudes. It is obvious that these aftereffects could well cause trouble in flying at lower levels and also in landing.

Nearly all observers agree that the organ of hearing is the most resistant of all to anoxia, and, for practical purposes, it probably functions until psychomotor collapse occurs.

The sense of touch is probably somewhat affected at altitudes beyond 18,000 feet, but this is of no great practical importance.

Nothing authoritatively can be said about taste and smell. While, for practical purposes, the effect of anoxia on these two senses is not especially important, nevertheless, as previously mentioned, a study of anoxia on these might provide a better understanding in certain disorders of these two senses.

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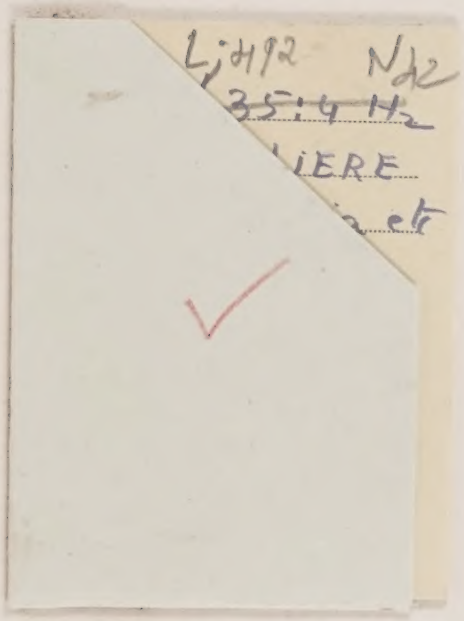
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